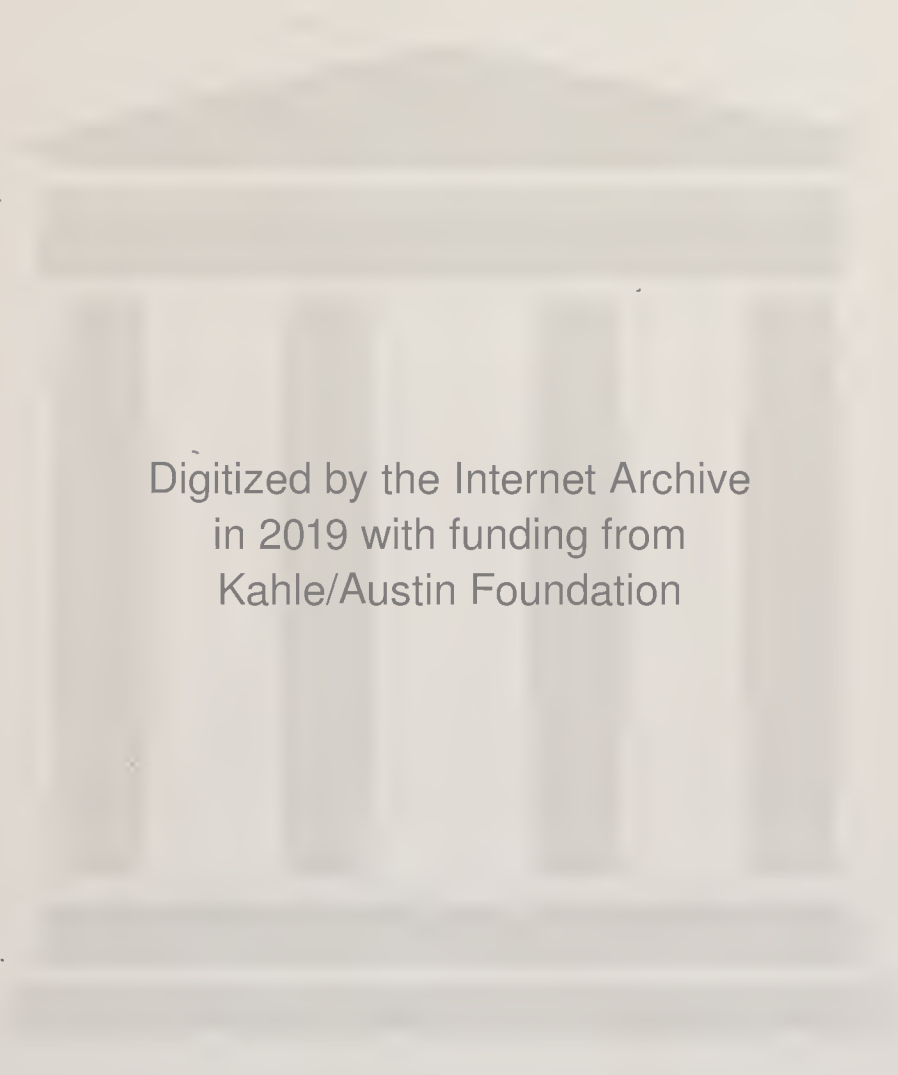


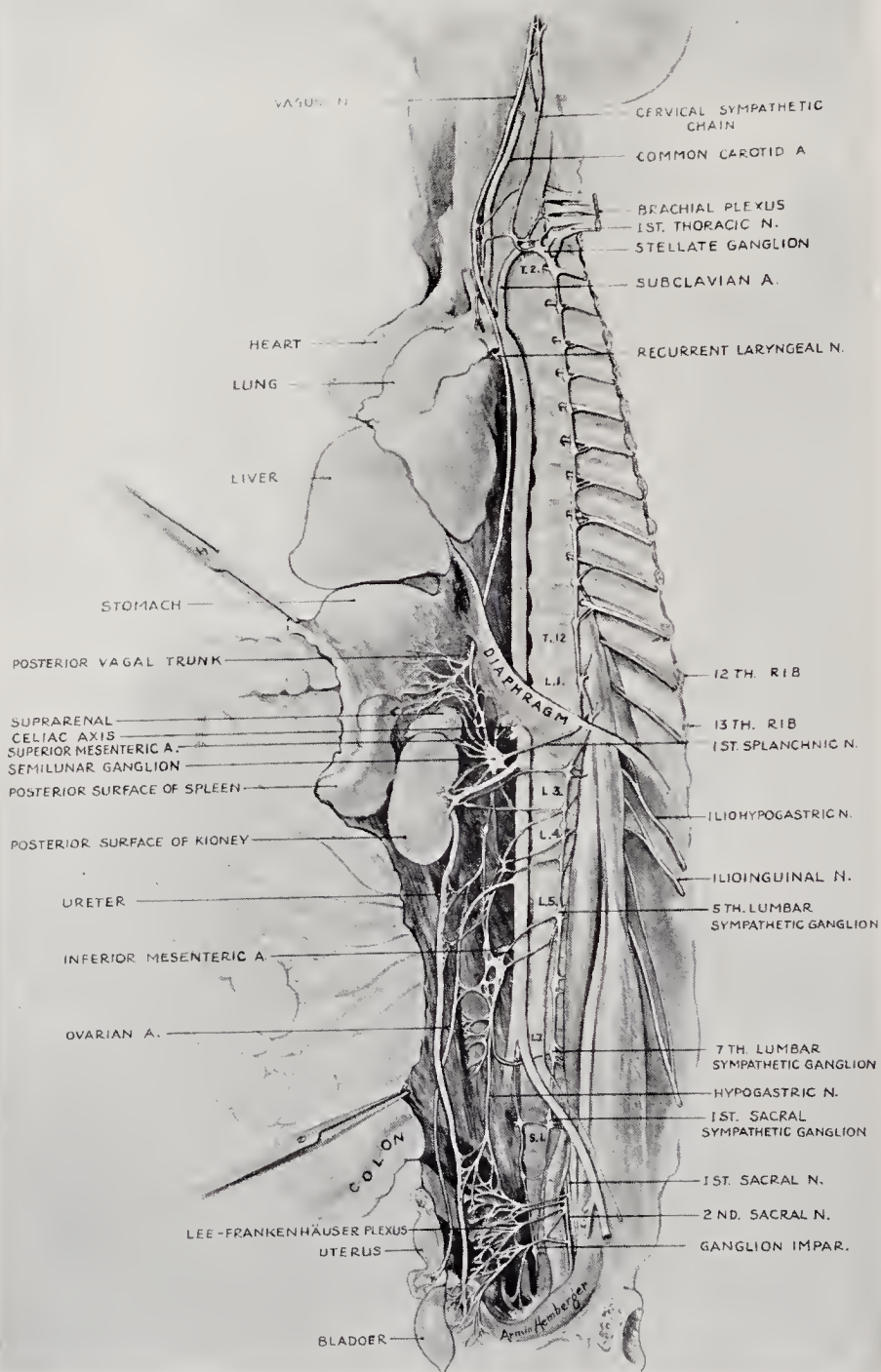
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Autonomic Nervous System of a Monkey
(*Macaca mulatta*; from Zuckerman, 1938.)

PHYSIOLOGY OF THE NERVOUS SYSTEM

BY

JOHN FARQUHAR FULTON

M.A., D.Phil., D.Sc. (Oxon.), S.B., M.D. (Harv.)

Sterling Professor of Physiology, Yale University

Formerly Fellow of Magdalen College, Oxford

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PREFACE TO SECOND EDITION

MANY new and significant disclosures have been made during the five years since this book was first published, and in now revising it I have attempted to incorporate as much of the new material as possible without expanding the book unduly. The revision has, however, been completed under distracting circumstances of war, and no doubt important work published from various belligerent countries has failed to receive notice; for this I can only hope to make amends if another edition is called for after international communications have been re-established. Many chapters have been largely rewritten; others such as chapter xv on cerebral cytoarchitecture have been left substantially in their original form.

The central nervous system looms large in war time when injuries of the whole cerebrospinal axis, as well as of peripheral nerves, occur in large numbers; such injuries take origin not only from mechanical, chemical and nutritional insults but they also arise from exposure to low oxygen tensions, high accelerations and other stresses created by the fast-moving engines of modern warfare. Fortunately the biochemical approach to the physiology of the nervous system has been notably advanced during the past five years, and this has served to throw light on many of the injuries and stresses peculiar to war. In a textbook for students the fundamentals cannot be neglected, but in these critical times it has seemed essential to emphasize practical applications from the outset.

Another advance, largely in the biochemical sphere, springs from the accumulating evidence that acetylcholine — once proclaimed as the universal synaptic transmitter — and its enzyme choline esterase must take a far more important position in the physiology of the nervous system than was first anticipated, even by the most ardent protagonists of chemical transmission. Acetylcholine and choline esterase are not peculiar to the synapse; actually they exist along the entire neuronal surface — axoplasm and probably soma — and they are evidently essential to the metabolism of all nerve cells. The latest studies of Nachmansohn indicate that the choline esterase enzyme system is in fact an inte-

gral part of the mechanism responsible for the development and propagation of the action potential. Thus the wide differences once believed to exist between the proponents of electrical, as opposed to chemical, transmission of nerve impulses have largely disappeared.

One can point to progress in many other directions. Perhaps most significant have been the developments inaugurated by the late J. G. Dusser de Barenne and his colleagues, Warren McCulloch, Hugh Garol, Gerhardt von Bonin and Percival Bailey, through analyzing in higher primates the inter-action of various areas of the cerebral cortex and basal ganglia upon one another; the studies of cerebellar localization of Robert Dow and Gervase Connor may also be mentioned. In the sphere of the parietal and occipital lobes the work of Clinton Woolsey, Wade Marshall, Earl Walker, Talmage Peele and Theodore Ruch are noteworthy. One must also mention the signal advances stemming from functional isolation of single nerve units: Detlev Bronk, Sarah Tower and Hallowell Davis who have placed single sensory units under direct observation; Derek Denny-Brown, David Lloyd, John Eccles and associates Stephen Kuffler and Bernhard Katz, Birdsey Renshaw, Harry Grundfest and Herbert Gasser, single motor units, peripheral and central. In the developmental sphere the work of Marion Hines and Margaret Kennard on infant monkeys and chimpanzees has required special notice. Finally, the brilliant work of Robert F. Pitts on the respiratory centres must be mentioned and in the realm of cutaneous receptors and their regeneration the work of the late H. H. Woollard, Graham Weddell, John Z. Young and Paul Weiss which has given a vast store of new knowledge.

For reasons of economy, as well as aesthetic considerations, the type face for the present edition has been changed from Caslon to Granjon; some illustrations have been omitted, others added; and bibliographical references are now cited by year instead of by number, which has greatly expedited the revision and has made possible the addition of new references to the proof with a minimum of difficulty. Many references to studies superseded by more recent work have been omitted.

I desire especially to thank those who have read various parts of the revision, and others who during the past five years have sent corrections and suggestions. They are too numerous to mention, but I must especially thank Drs. David C. P. Lloyd, Rafael Lorente de N  , Earl Walker, Donald Marquis, Theodore C. Ruch, Margaret A. Kennard and David

Nachmansohn for assistance in chapters respectively on central inhibition, the thalamus, the occipital lobes, cytoarchitecture, the parietal lobes, the basal ganglia and acetylcholine(ch. III); and Dr. Donal Sheehan who assisted materially with the revision of chapters I and II and who has rewritten chapter XII; and finally to Dr. H. S. Liddell who has contributed a new chapter on conditioned reflexes. To Mrs. John P. Peters I must extend my thanks for much help in preparing the copy and reading the proof; and to Mrs. E. C. Hoff who assisted in compiling the indices.

J. F. F.

Yale University, March, 1943.

PREFACE TO FIRST EDITION

THE present monograph is essentially an exposition of the experimental physiology of the nervous system in which material has been assembled that will aid those whose ultimate objective is the study of Clinical Medicine. Since there are few recent works dealing with the functions of the central nervous system, I hope the volume may fill a need both in the medical student's curriculum and in the broad fields of Physiology and Neurology. Throughout the text emphasis is placed upon two important concepts, one old, one new. The first is the evolutionary principle of levels of function, which implies that headward segments of the brain have become dominant over caudal, and that when higher parts are removed many activities of lower segments are, after a time, "released" and can then be more readily analyzed. Study of these activities indicates that each level is organized to govern specific *functions* rather than to control anatomical units — movements rather than muscles. Thus the regulation of the blood pressure and the control of body temperature are functions which have fragments of their total mechanism represented at each level, from spinal cord to cerebral cortex. The same is true of sexual and other basic patterns of reaction, and there is no better way for a student to gain insight into the workings of the intact nervous system than to trace these individual mechanisms from segmental to the suprasegmental regions of integration. He should remember however that in man, owing to gradual "encephalization," a greater number of functions have been taken over by the cerebral cortex than in other mammals.

The second, and newer, concept relates to the extensive interaction normally occurring between somatic and autonomic reflexes. The autonomic division of the nervous system can no longer be regarded as a purely peripheral system, but rather as an elaborately organized division of the central nervous system with representation in all levels. At each level, moreover, the somatic and the autonomic systems dovetail with one another, and while the somatic may predominate in a given region — and thus obscure the autonomic component — it is generally impossible to evoke a somatic reflex that does not have an autonomic con-

comitant of central origin. This is notably true in the spinal cord (*e.g.*, the "mass" reflex), in the medulla (consider the vasomotor accompaniments of nociceptive reflexes), in the hypothalamus (heat regulation includes panting and shivering, as well as sweating and vasomotor control), and at the striatal and cortical levels where the intermingling of somatic and autonomic reactions is even more extensive (ch. xxiii). When, therefore, the intact nervous system is visualized, a mental picture is conjured up of two great interlacing mechanisms — which share some receptors in common but which have others that are specific — and which discharge together in a synergic manner that makes for unification of reaction in the organism as a whole.

Particular attention has been devoted to primate forms, since, owing to greater encephalization, experimental evidence drawn from the primates is more immediately applicable to the human being than that drawn from studies of other mammals. Because it is deemed unwise to approach any phase of function without a solid background of morphology, nearly a third of the book is devoted to considerations of structure. The recent developments in neuro-anatomy have been particularly stressed, notably in the domain of the receptors, the dorsal and ventral nerve roots, the structure of the synapse, the cerebellum, thalamus and its cortical projections, hypothalamus and the finer structure of the cerebral cortex. Small type has been used for the historical notes at the beginnings of chapters, for anatomical description and for controversial details, and the student may wish to postpone examination of such passages until a second reading. Each chapter concludes with a detailed summary in which the substance of the chapter is presented, usually in somewhat different sequence than that followed in the text.

J. F. F.

Yale University, June, 1938.

CONTENTS

I. THE RECEPTORS	1
II. DORSAL SPINAL NERVE ROOTS AND THE DERMATOMES . . .	18
III. THE MOTOR UNIT	37
IV. SYNAPSES AND ELEMENTARY REFLEXES	51
V. CENTRAL INHIBITION	81
VI. THE SPINAL CORD: FLEXION REFLEX	91
VII. THE SPINAL CORD: EXTENSION REFLEXES	103
VIII. THE SPINAL CORD: INTERSEGMENTAL REFLEXES. SPINAL MAN	118
IX. THE MEDULLA OBLONGATA: DECEREBRATE RIGIDITY . . .	143
X. THE MEDULLA OBLONGATA AND MIDBRAIN: POSTURAL RE- FLEXES	163
XI. THE PONS AND MIDBRAIN: OPTIC REFLEXES	180
XII. AUTONOMIC NERVOUS SYSTEM	189
XIII. THE HYPOTHALAMUS: AUTONOMIC REGULATIONS . . .	223
XIV. THE THALAMUS	252
XV. CEREBRAL CORTEX: ARCHITECTURE, INTRACORTICAL CONNec- TIONS, MOTOR PROJECTIONS	274
XVI. CEREBRAL CORTEX: THE OLFACTORY SYSTEM	314
XVII. CEREBRAL CORTEX: THE OCCIPITAL LOBES AND VISUAL SYS- TEM	321
XVIII. CEREBRAL CORTEX: THE TEMPORAL LOBES	337
XIX. CEREBRAL CORTEX: THE PARIETAL LOBES AND SOMATIC SEN- SATION	348
XX. CEREBRAL CORTEX: THE MOTOR AREAS AND PYRAMIDAL SYS- TEM	369
XXI. CEREBRAL CORTEX: EXTRAPYRAMIDAL AND INTRACORTICAL PROJECTIONS	394
XXII. CEREBRAL CORTEX: THE FRONTAL ASSOCIATION AREAS . .	418
XXIII. CEREBRAL CORTEX: AUTONOMIC REPRESENTATION . . .	429
XXIV. THE EXTRAPYRAMIDAL MOTOR SYSTEM: BASAL GANGLIA .	445
XXV. THE CEREBELLUM	463
XXVI. THE NERVOUS SYSTEM AS A WHOLE: THE CONDITIONED RE- FLEX	491
BIBLIOGRAPHY AND AUTHOR INDEX	523
SUBJECT INDEX	591

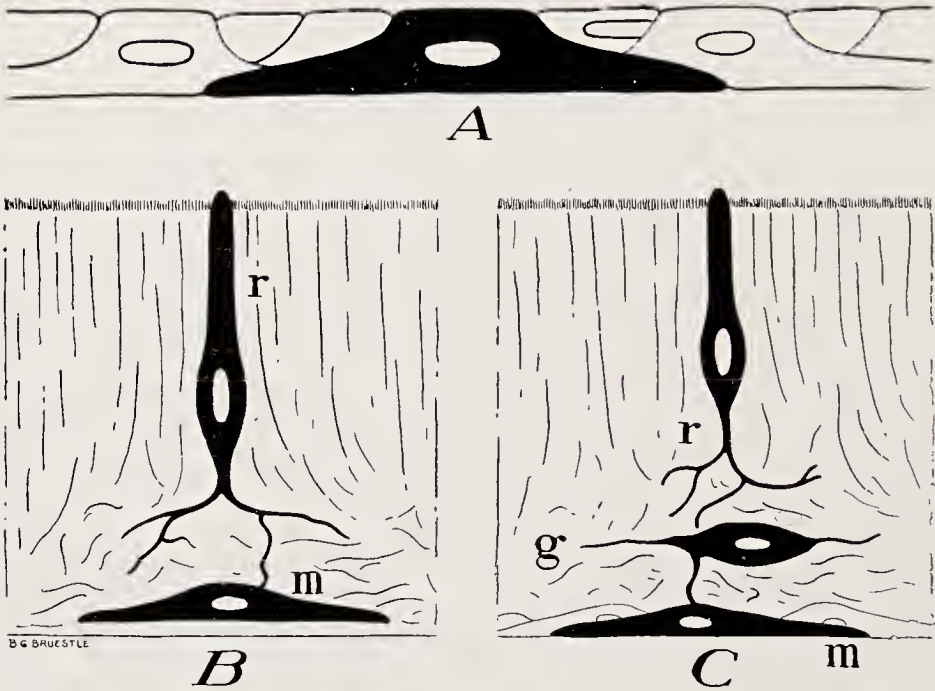


FIG. 1. Parker's diagram of the elementary nervous system. A, The independent effector (muscle cell of a sponge). B, the receptor-effector system in tentacles of a sea anemone; *r*, sensory cell; *m*, muscle cell. C, A more complex receptor-effector system with an intermediate ganglion cell, *g*, interposed between receptor and the muscle cell. Also from a sea anemone (redrawn from G. H. Parker, *The elementary nervous system*, Lippincott, 1919).

I

THE RECEPTORS

UNICELLULAR animals “react” to changes in their external environment by movements which often affect the entire cell. If the environmental change should be local—a mechanical “stimulus” to an amoeba’s pseudopodium—the pseudopod is withdrawn, and, after an interval, the whole organism may contract into a spherical mass by virtue of a change propagated over its cellular surface. In multicellular organisms, even in simple forms such as sponges and coelenterates, special cells have been developed to respond *directly* to changes of the external environment; these executant units have been designated by Parker “independent effectors”(fig. 1A). During evolutionary development “receptor-effector” systems appear, the receptor element being in the nature of a sensory cell or surface(fig. 1B, *r*)which lacks motor function. These sensory areas ultimately become responsive to *specific* environmental changes; thus some may be more readily affected by light, others by vibration, still others by heat, etc. These specialized cells in multi-cellular organisms came to be designated “receptors” because they are designed to receive particular qualities of stimuli. The various sense organs thus serve to sort out different stimuli, and to convey appropriate reports concerning them, either to an “effector”(fig. 1B, *m*), or to a central “adjustor” ganglion cell(fig. 1C, *g*). In man, the various sense organs are adapted for the reception of an extraordinarily large variety of environmental changes—touch, heat, cold, light, sound, taste, smell, etc.

In entering upon a study of the nervous system, it is logical to begin with the pathways into the spinal cord and brain. These pathways commence with the receptors and continue, via the *afferent* nerve fibres, to the dorsal root ganglia and into the spinal cord, or, in the case of the head, to analogous ganglia of the brain itself. Our first problem, therefore, is to classify and study the general characteristics of receptors; the special characteristics of individual sense organs will then follow, and finally their mode of transmitting messages to the central nervous system will be described.

TYPES OF RECEPTOR

Human beings experience different types of sensation and it has become abundantly clear that each modality of sensation is subserved by structurally different types of sensory nerve ending, *e.g.*, the endings for pain, touch, cold and warmth are specific and distinguishable. The sensory receptors of the body as a whole are divided into two primary groups: (i) the exteroceptors, and (ii) the interoceptors.* In the first group are included cutaneous, chemical and the distance receptors. For the purposes of the present chapter, consideration will be restricted to the cutaneous exteroceptors, since the distance receptors involve the nerves of special sense — vision and hearing — as do the chemical receptors — smell and taste (Sherrington, 1906a). The physiology of the special senses is beyond the scope of the present volume.

EXTEROCEPTORS. These end organs include a great variety of specialized and unspecialized sense organs, many of which are peculiar to the skin and its appendages. There are touch corpuscles, endings for heat and cold sensibility, and the free nerve endings which in higher animals subserve pain. They may be grouped into two categories: (i) free nerve endings, including the sensory nerve nets (Woollard, 1936, 1937; Weddell, 1941a); and (ii) encapsulated endings such as those of Meissner, Krause, Ruffini, etc. The morphological features and distribution of these several types of ending have recently been studied in detail by Weddell and his colleagues and attention should also be directed to the excellent critical review of Walshe (1942).

Free nerve endings and plexuses (Pain). The most widely distributed receptors in the body are the free nerve endings and the unmyelinated plexiform networks deep in the epidermal and dermal layers of human skin; these undifferentiated endings also occur in blood vessels and in many visceral organs (see Kuntz and Hamilton, 1938). The endings come both from small myelinated and from unmyelinated nerve fibres, the latter often penetrating the epidermis (Woollard, Weddell and Harpman, 1940). Histological studies of Boeke (1932) and others suggest that these endings may terminate, not between cells, but actually *within* the cyto-

* Sherrington (1906a) is responsible for the excellent terms "exteroceptor" and "interoceptor." In his original definition both were related to the *surface fields* of the body, the exteroceptors innervating the external surface of the body and the interoceptors, the internal surface, *i.e.*, the gastro-intestinal tract. Current usage, however, has broadened somewhat the connotation of the interoceptors to include *all* of the internal receptor fields including the proprioceptors and the visceroreceptors (see below). Another useful mode of classifying receptors is into: (i) somatovereceptors with subdivisions of: (a) exteroceptors and (b) proprioceptors, and (ii) visceroreceptors. This classification can be interchanged with the one here given without confusion.

plasm of the cells (fig. 2A). In the cornea of the eye, in which free nerve endings are present, pain is said to be the only, and is certainly the principal, modality of sensation that can be perceived (see Tower, 1940). The adequate stimulus for pain is any noxious agent which tends to cause tissue or cellular destruction. The end organs of pain are therefore designated "nociceptors," and the reflexes arising from such receptors are referred to as "nociceptive."

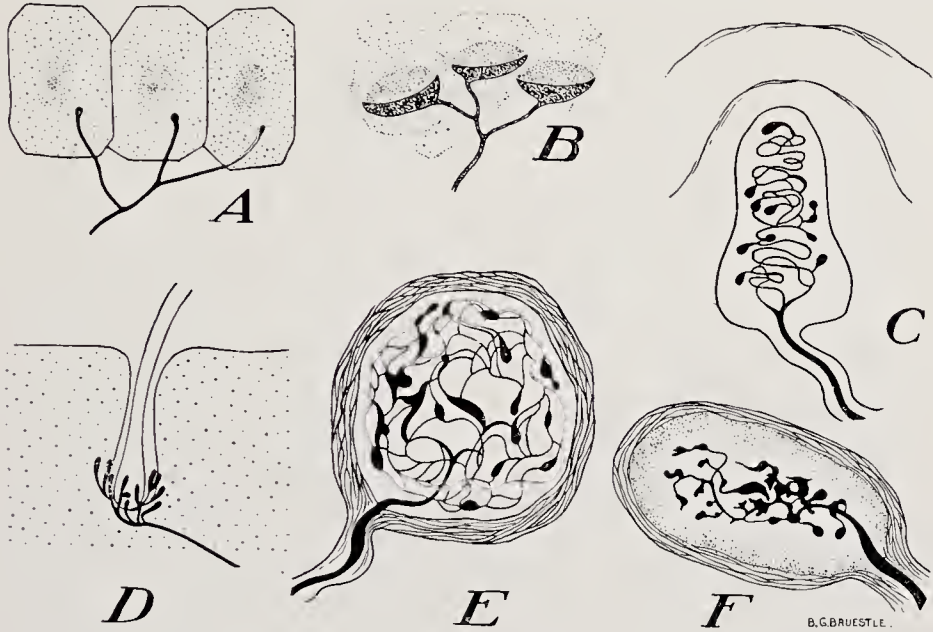


FIG. 2. A diagram of the principal cutaneous receptors. The structure of all of these end organs is highly variable and the individual drawings are schematic. A, Free nerve endings from the cornea of the eye. Note that the nerves terminate within the cell. Similar endings are found in the skin. Others terminate as networks (Woollard). B, Merkel's tactile disc (from the pig's snout). C, Meissner's tactile corpuscle. D, Basket-ending at the root of a hair follicle. E, End bulb of Krause from human conjunctiva. F, Golgi-Mazzoni corpuscle from human skin (Pressure).

The widespread distribution of these nociceptive fibres has recently been described by Weddell (1941a) in the skin of man and monkey. A single terminal fibre — unmyelinated or small myelinated — usually ends in a knobbed loop about 1.5 mm. in diameter (fig. 3). There is commonly a similar loop at the same skin focus overlapping the first but situated in another plane. "Each unit of skin," Weddell observes (p. 364) "is innervated by more than one fibre of the same type whose endings interlock with each other. In fact each unit of skin is innervated by a number of fibres which approach the area from all directions." As evidence of the punctate character of the pain response in human skin he cites (p. 355) a human case from which "A piece of skin 2 by 3 cm. was stained and removed. . . . In the area from which pain alone could be aroused fine nerve fibres were seen giving rise to superficial nerve nets; no thick fibres or organized endings were seen. On the other hand, in the area of skin on which both pain and touch could be aroused, the cutaneous nerve plexus was seen together with thick nerve fibres around hairs and thinner fibres giving rise to superficial nerve nets." In keeping

with this Tower(1940)has been able to show by electrophysiological methods that the terminal ramifications of a single afferent fibre from the rabbit's cornea comprise a unit area of from 50 to 200 sq. mm. and that the area has sharply circumscribed limits. She suggests the term "sensory unit" for such terminations, in parallel to "motor unit"(ch. 11). A sensory unit is thus made up of a dorsal root ganglion cell and all the end organs which, through bifurcation, it may innervate (cf. Walshe, 1942, p. 109).

Merkel discs, Meissner's corpuscles and hair-root endings(Touch). Three discrete receptors, all responding to mechanical deformation of the skin and hence subserving tactile sensibility, have widely different morphological structure. Merkel's tactile cells are found in the snout of pigs and other mammals, in the finger tips, glans penis, mucous membrane of mouth and lips, and erratically distributed elsewhere in cutaneous surfaces of the body. They consist of cup-shaped terminal discs(fig. 2b), reticulate in structure, and generally several of the sensory discs are innervated by a single fibre. These end organs, unlike the free nerve endings, are extracellular and they may have accessory autonomic innervation.

Meissner's corpuscles are more highly organized structures than the Merkel discs(see fig. 2c). The terminal sensory ending ramifies in an irregular spiral which is surrounded by a connective tissue capsule. These corpuscles occur throughout the cutaneous surface of man, being numerous in the hand, foot, nipple and lip, and also in mucous membrane of the tip of the tongue; they receive a thin unmyelinated accessory innervation, presumably from the autonomic system. The actual morphology of the corpuscles varies widely in different parts of the body, but in any given part, *e.g.*, the nipple, the structure is generally constant. A given touch spot on the skin of the human finger "is commonly innervated by two or three nerve fibres, approaching from different directions, and ending in separate Meissner's corpuscles"(Weddell, 1941b, p. 444). Grandry's corpuscles in the skin of the duck's bill appear to be highly organized modifications of Meissner's cells.

The sensory terminals of the hair follicles are specialized tactile receptors, responsive to movements of hair; they are best developed in the vibrissae of night-roaming animals. They consist of a basket ending generally surrounding the base of a hair follicle, extending up toward the surface of the skin(fig. 2d). The arrangement of the ending varies widely, but it is obviously disposed to respond to mechanical displacement of the hair.

Krause's end bulbs(Cold). Krause's end organs, which are distributed in the skin, are also difficult to describe and can best be visualized from a diagram(fig. 2e.). The nerve passes into a spherical connective tissue capsule and there ends in a complex series of S-shaped loops intertwining one with the other. Goldscheider originally insisted that Krause's bulbs coincided with cold spots, and although this has been contested by Dallenbach(1927)and others(see Lanier, *et al.*, 1935), Weddell(1941a)has lately adduced convincing histological evidence that they are in fact the cold receptors. A biopsy specimen of a cold spot from the forearm of the late Professor Woollard revealed two groups of Krause's end bulbs at a point 1 mm. immediately beneath the cold spot(Weddell, 1941a, p. 355). A composite diagram of the various end organs in human skin from Weddell *et al.* is given in figure 3.

Corpuscles of Ruffini(Warmth)and Golgi-Mazzoni(Pressure). This group of sensory end organs has a somewhat simpler structure than the end bulbs; they are also encapsulated, but the nerve executes fewer loops and appears to expand into a series of small spherical and wider flattened enlargements indicated diagram-

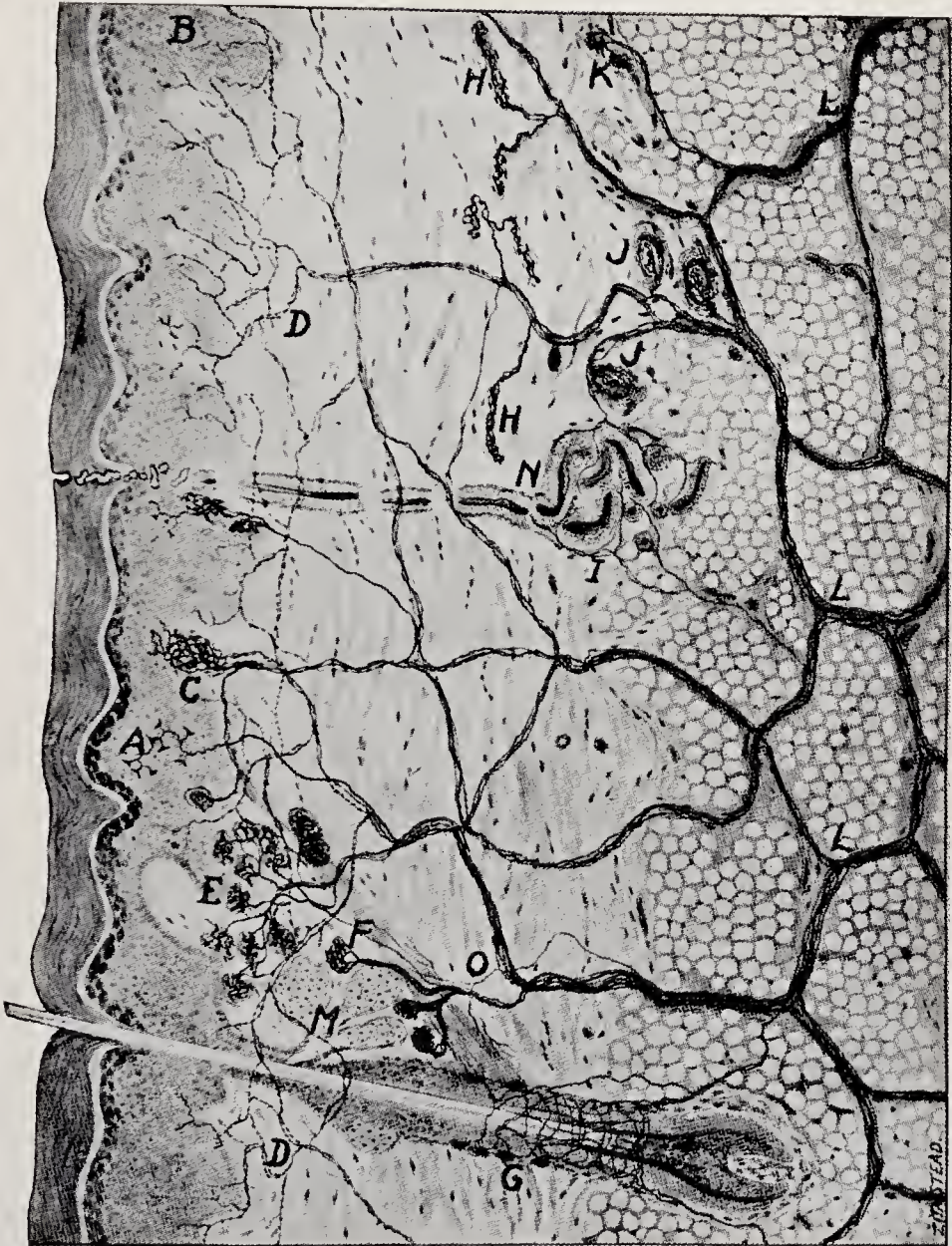


FIG. 3. Composite diagram showing the innervation of the human skin. A, Merkel's discs, subserving touch. B, Free endings, subserving pain. C, Meissner's corpuscles, subserving touch. D, Nerve fibres, subserving pain. E, Krause's end bulbs, subserving cold. F, Nerve-endings, subserving warmth (sometimes called Ruffini's endings). G, Nerve fibres and endings on hair follicle, subserving touch. H, Ruffini's endings, subserving pressure. I, Sympathetic nerve fibres innervating sweat glands. J, Pacinian corpuscles, subserving pressure. K, Golgi-Mazzoni endings, subserving pressure. L, Nerve trunks containing thick and thin fibres. M, Sebaceous gland. N, Sweat gland. O, Sympathetic fibres supplying erector pili muscle. Drawing composed from methylene-blue and silver preparations. (From Woollard, Weddell and Harpman, *J. Anat.*, 1940, 74, 427.)

matically in figure 2F. Weddell believes that the Ruffini and Golgi-Mazzoni types of end organ are responsive to warmth and pressure, respectively. The categorical allocation of warmth perception to Ruffini corpuscles is often disputed for, as Sheehan(1933)points out, there are many intermediate types of encapsulated end organ: "Between the largest Pacinian corpuscles that are plainly visible to the naked eye, and those of Golgi-Mazzoni, which can only be detected with the microscope, there is an uninterrupted series of intermediate or transitional forms. And from the so-called genital corpuscles there is a further gradual transition to the more elaborate corpuscles as described by Golgi and Mazzoni. Thus we have to remember in ascribing any particular function to one type of end-organ that there are all grades of corpuscles between the typical Pacinian and the other similar lamellated corpuscles." The Pacinian corpuscles which occur in the dermis and in the viscera will be described below with the visceroreceptors.

These three groups of endings: free nerve terminals, tactile and pressure corpuscles, and the several other encapsulated corpuscles confer upon the skin of intact human beings sensibility to pain, touch and thermal change. A re-examination of their distribution and correlation with sensory perception has recently been made by Woollard, Weddell and Harpman(1940)who emphasize anew that the reaction of these highly organized receptors is definitely specific, *i.e.*, from Meissner's corpuscles it is impossible to evoke pain; indeed, one can insert a needle into one of these corpuscles and so cause intense stimulation without evoking conscious sensation other than that of touch or pressure. This principle of specificity of sensory perception from individual end organs is generally known as the law of "specific nerve energies"; it was first enunciated by Charles Bell(1811)and later and more completely by Johannes Müller(1826). Stimulation of a given sense organ, Müller said, gives rise to its own particular sensation and to no other. This concept lies at the basis of all modern interpretations of the nervous system (Walshe, 1942).

INTEROCEPTORS. The interoceptive group of sense organs comprises all endings of the internal receptive field(see footnote, p. 2)and is made up of two large sub-groups:(i)the proprioceptors, which are concerned with muscle and position sense, and(ii)a special group supplying the viscera and blood vessels which give rise to local visceral and vascular reflexes and to conscious sensations of hunger, thirst, sexual desire and kindred perceptions.

Proprioceptors. The proprioceptors are highly organized somatic sensory end organs situated in the semicircular canals(ch. x), and in the muscles, tendons and joints. As originally defined by Sherrington(1907a) the proprioceptors are those end organs which are stimulated by "ac-

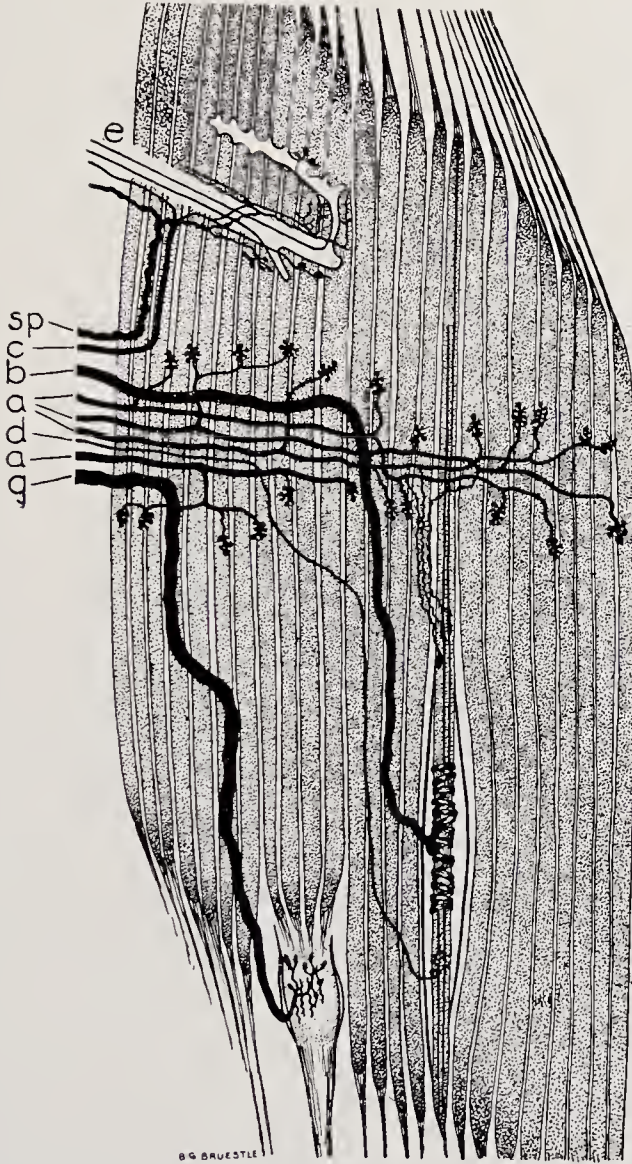


FIG. 4. Denny-Brown's diagram illustrating the sensory and motor innervation of a group of 23 mammalian muscle fibres. The motor innervation comes from 4 fibres, *a, a, a, a*; the muscle spindle is made up of 3 intrafusal fibres, each one innervated by branches of motor nerve fibres *a, a, a, a*. The spindle has one large annulospiral ending, *b*, and a single flower spray ending connected with the nervous system by a fibre of relatively small diameter, *d*. There is a single Golgi tendon organ, *g*, and a sympathetic plexus, *sp*, accompanied by a small myelinated pain fibre, *c*, from the blood vessel, *e* (Creed, Denny-Brown, *et al.*, *Reflex activity of the spinal cord*, Oxford Press, 1932).

tions of the body itself." They include those of muscle and labyrinth, as well as those in the viscera which are responsive to the position of the body in space. In recent years the end organs of the vascular system and viscera, which strictly speaking are "proprioceptive" in the sense of being stimulated by the body itself, have been segregated into the special category of visceroreceptors. The morphological characteristics of the somatic proprioceptors may be briefly described.

Muscles are equipped with three types of ending: (i) the muscle spindle, (ii) Golgi tendon organ and (iii) Pacinian corpuscles. In addition, the blood vessels of most muscles are provided with (iv) free nerve endings subserving pain.

Muscle spindle (Stretch afferents). The muscle spindle, a structure named by Kühne (1863), proved sensory by Sherrington (1894), and first adequately described by Ruffini (1892, 1898), is a highly organized complex of sensory end organs and muscle fibres which lies within the fleshy substance of muscle and embraces one or more modified red muscle elements generally called "intrafusal fibres." The principal nerve ending forms an annular band which spirals irregularly around the intrafusal fibres in their equatorial region (fig. 4, *b*); the whole ending, including the greater part of the intrafusal fibres, is invested with a connective tissue capsule containing tissue fluid. The capsule itself has no other nerve supply (*i.e.*, no autonomic fibre), but the intrafusal fibres have motor innervation (fig. 4, *a, a*) and a secondary "flower spray" sensory ending (fig. 4, *d*), which is probably connected with the nervous system by a middle sized medullated fibre separate from that of the large fibre of the annulospiral ending. The "annulospiral" and "flower spray" endings both degenerate when appropriate posterior root *ganglia* (see ch. 11) are removed (Hines and Tower, 1928), which establishes their sensory origin. The remaining innervation is somatic motor, since it disappears when the ventral nerve roots are cut (Hinsey, 1927); in these circumstances the intrafusal fibres also undergo atrophy and ultimately (after a year) degeneration (Tower, 1939). Muscle spindles are found in all antigravity muscles, and in some of the flexors, but they do not occur in the extraocular muscles (Sherrington, 1894, 1897; Hines, 1927).

Mechanically the muscle spindle lies "in parallel" with the active constituents of the muscle. If, for example, the muscle should be stretched passively, the muscle spindle would be affected; whereas if the surrounding muscle fibres contracted the stretch stimulus would no longer be effective upon the intrafusal fibres since the tension would be maintained by the active cells (fig. 5). For this and for other reasons, muscle spindles have been regarded as "the stretch afferents" (Fulton and Pi-Suñer, 1928; Matthews, 1931, 1933).

Golgi tendon organs (Tension recorders). The tendon endings are specialized structures surrounding the distal ends of small groups of muscle fibres (fig. 4, *g*); they are also undoubtedly responsive to stretch, but these endings can make no distinction between active tension and passive tension. Thus, if the muscle is stretched passively, the tendon organs are affected, and if the muscle contracts, they, unlike the muscle spindles, are also affected because they are arranged "in series" with the tension producing units. A diagram illustrating this differing arrangement is given in figure 5.

Pacinian corpuscles (*Deep pressure*). The Pacinian end organs are classified with the proprioceptive group, since they occur most commonly in tendon sheaths, muscle aponeuroses, intramuscular septa, periosteum, peritoneum, pleura, pericardium, mesentery and also, to a certain extent, in the deeper part of the dermis of the hands and feet. They are responsive to mechanical deformation and are regarded as endings of deep pressure sensibility and they possibly respond to gravitational drag on the mesentery. In structure they resemble an onion with concentric layers of fibrous tissue capsule and a knotted central nerve fibre. The accessory unmyelinated innervation is probably vasomotor in origin (Hinsey, 1928).

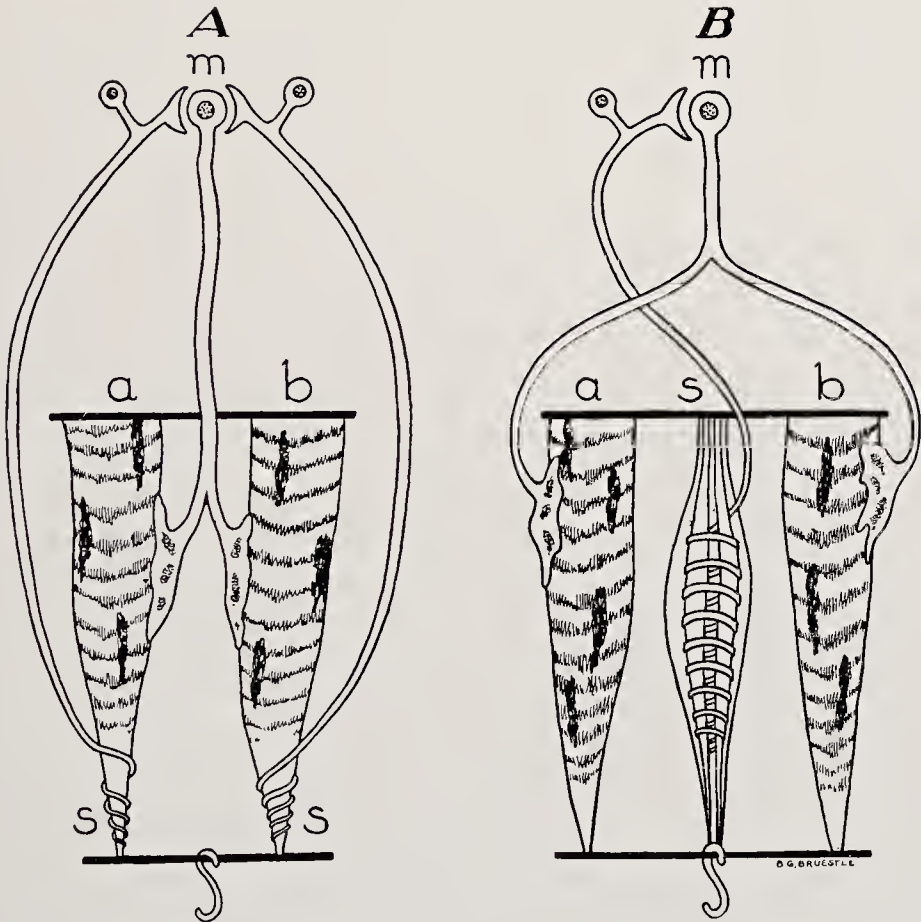


FIG. 5. Diagram showing the two principal types of end organ in skeletal muscle. In A the tendon organs are disposed "in series" with the tension-supporting elements. Such endings make no distinction between active and passive tension; *a*, *b*, skeletal muscle fibres, *m*, motor horn cell, *s*, sensory end organ. In B a diagram of a muscle spindle, showing the conditions obtaining when the end organ lies "in parallel" with the tension-supporting elements. When muscle fibres *a* and *b* contract, they take up any tension which may previously have been exerted upon *s*, the muscle spindle (Fulton and Pi-Suñer, *Amer. J. Physiol.*, 1928, 83, p. 556).

Free nerve endings(Pain). The free nerve endings of muscles and viscera are similar to those elsewhere in the body. In the case of muscles they appear to be restricted to the blood vessels and aponeurotic sheaths; muscle pain is therefore due principally to spasm or rupture of the smaller vessels which carry this diffuse nociceptive innervation(Kellgren, 1938, 1939). In the gut, ureter and bladder the characteristics of the sensory innervation have not yet been well defined. Undoubtedly pain originating in these structures is partly mediated by unmyelinated fibres. The phenomenon of "referred pain," and the tendency for the skin over an injured or inflamed viscus to become hypersensitive, is probably explicable in terms of the extensive dichotomy of pain fibres, one branch passing to the skin, the other innervating a viscus in the corresponding dermatome(ch. II)(Weiss and Davis, 1928). Foerster(1927a) reports that on stimulating the peripheral cut end of a sensory nerve pain is felt in areas supplied by adjacent cutaneous nerves. Weddell(1941a), confirming this observation, finds that it is accounted for by the recurrent course taken by many of the smaller nerve fibres in mixed nerve trunks.

Autonomic endings. The only autonomic endings traceable to sensory end organs in muscle are those which accompany the free nerve endings to the blood vessels(fig. 4, *sp*), and those to the Pacinian corpuscles.

Visceroceptors. Sheehan(1932, 1933)has indicated that the mesentery is provided with large numbers of Pacinian corpuscles whose myelinated fibres pass to cell stations within the dorsal root ganglia. The viscera are also supplied with many small medullated fibres, generally ending in or about blood vessels in a variety of terminals. These have been fully studied and reviewed by Hinsey(1934). The majority of terminals, however, are free nerve endings, which, in other parts of the body, have been associated with pain reception. These endings also occur in the smooth muscles of the lungs and gut, the ureter and kidney pelvis, in bladder and genital tracts. The reflexes associated with stimulation of these endings will be discussed in the later chapters on the sympathetic nervous system, thalamus and cerebral cortex. There are also highly organized visceroreceptors in certain parts of the vascular system such as those in the carotid sinus(ch. II, XII).

From this cursory survey of the various types of receptor, it is obvious that, irrespective of classification in terms of the interior and exterior of the body, receptors may also be classified in accordance with the type of nerve endings, which in turn determines the type of fibre which they

send into the nervous system. In general, nerve endings that are structurally elaborate, such as muscle spindles (fig. 4, *b*) and Pacinian corpuscles, are connected with the nervous system by fibres of large diameter (fig. 10, receptors 1 and 2). The small myelinated fibres, on the other hand, often terminate as free nerve endings without elaborate receptors. Many lines of evidence to be mentioned later indicate that the free nerve endings are associated with pain. Their impulses are communicated more slowly to the nervous system. Hence a cut of the skin is first felt as a touch sensation and only later is pain reaction evoked. There are also unmyelinated sensory fibres with free nerve endings which likewise subserve pain sensibility.

GENERAL CHARACTERISTICS OF RECEPTORS

The receptor end organ is a specialized structure designed to set up nerve impulses in response to changes in the environment. As indicated above, these changes are referred to as "stimuli," which may be defined in Adrian's words (1928, p. 18) as "any change in the environment of an excitable tissue which, if sufficiently intense, will excite the tissue, *i.e.*, will cause it to display its characteristic activity. The stimulus is thus an external change and it may be ineffective—the stimulation may not have been intense enough to excite." In these circumstances no message of any sort is sent to the nervous system.

EXCITATION AND ADAPTATION. The characteristics of the excitability of peripheral nerves are fully dealt with in the volume on nerve and muscle of this series. The principles involved in excitation of an end organ are similar to those deduced from electrical stimulation of an isolated nerve trunk; here the stimulus, be it electrical, chemical or mechanical, produces a local alteration of sufficient intensity to develop a nerve impulse. The change must fall within a certain time interval and the rate at which the change occurs may be the determining factor in the effectiveness of a stimulus; a slow alteration, such as the gradual increase of intensity of an electric current, may cause no change at all in the end organ, because "the tissue adapts itself fairly rapidly to the change in its environment, so that excitation does not take place." Another possible explanation of the ineffectiveness of slowly applied stimuli takes us a little nearer the root of the problem. A rapidly increasing current may yield the necessary accumulation of ions in the nerve fibre, but "this accumulation leaks away almost as soon as it is produced. The

process may be compared with the occurrences described in the arithmetic books of our school days, where someone turned on the taps of a bath without taking the precaution of putting in the plug. Whether the bath would ever be filled or not would then depend on the rates of inflow and outflow and on the way in which these rates changed as the cistern emptied and the level in the bath began to rise "(Adrian, 1928, p. 20). This process, in the case of sensory end organs, is generally referred to as "adaptation" (see pp. 14-18) and is one of the characteristics common to all sense organs.

INTENSITY. Once a stimulus to an end organ is effective, it sets up a single, or, more likely, a train of nerve impulses in the nerve fibre which it serves. With the more highly organized end organs, there is a one-to-one ratio between end organ and dorsal root ganglion cell, *i.e.*, each end organ has its own private pathway to the nervous system. Since an end organ must convey its messages to the nervous system by the all-or-nothing nerve impulse, *the only possible way of communicating differing intensities of stimulation from a single end organ lies in differing rates of discharge.* The single end organ, if strongly stimulated, will set up a more rapid series of impulses than if the stimulus were less intense. Intensity, however, may also affect the *duration* of the repetitive discharge in the end organ. Thus, if the duration of application of the stimulus is constant, but the intensity of the stimulus increased, the end organ may continue firing for an increasingly long period after the stimulus has ceased. The reflex arc makes use of rapid rates of afferent discharge to secure more intense reflex action.

A rapidly adapting sense organ will be a poor recorder of intensity since the rate will not be a function of strength of stimulation but rather of its duration. Muscle spindles and pressure receptors adapt little, hence while discharging continuously they will be sensitive to slight changes of intensity and *will signal such*. Touch receptors, being rapidly adapting, are poor for signalling grades of intensity.

A changing environment, however, seldom affects single end organs, so the nervous system has yet another means of dealing with stimuli of varying intensity, namely, through variation in number of similar sense organs set off by a given stimulus. Thus, if two closely adjacent pain endings are stimulated, the reflex effect may be considerably greater than if either one is stimulated alone, even though stimulated at maximal intensity (Adrian, 1932). The increased effect of stimulation of more

than one end organ of a similar type involves *spatial* summation, whereas the increased reaction caused by repetition of stimulation of the same end organ brings about *temporal* summation of impulses. The nervous system makes use of the rapidly adapting touch receptors to interpret intensity, whereas temporal summation is more common in slowly adapting muscle receptors.

To summarize, since the nerve fibre connecting the end organ with the spinal cord fires maximally or not at all (all-or-nothing principle), the stimulus is merely a trigger which sets off the impulse, and it does not contribute the energy essential for its conduction. The character of the impulse is thus quite independent of the intensity or character of the stimulus which set it up. All end organs therefore share this second point in common, namely, that they convey their effects to the nervous system by the same kind of impulse.

SPECIFIC RECEPTORS

A few examples illustrating these general principles may be cited. The following are taken from Adrian whose conspicuous success in placing single sensory end organs under direct observation has led to one of the principal advances in modern neurophysiology. Action currents from a single sensory nerve fibre have been magnified by Adrian and his pupils by valve amplification, and recorded either with a capillary electrometer or by a Matthews oscillograph.

MUSCLE END ORGANS. The sterno-cutaneous muscle of the frog is supplied by a nerve containing from 15 to 25 nerve fibres. Of these only 2 or 3 fibres appear to be sensory and, since the muscle itself contains, as a rule, only one muscle spindle, the single nerve fibre with which it communicates can be stimulated by stretching the muscle as a whole. When it contains more than one, the muscle can be dissected down until only one sensory fibre responds. It has been found that the impulses evoked by stimulating this single sensory unit recur at a frequency of *ca.* 30 per sec. The frequency varies with the strength of the stimulus and the time during which it acts. In this preparation the stretch stimulus is constant; it is interesting that the rate of discharge diminishes somewhat with time even though the muscle is under a constant stretch (1 gm. weight)—an illustration of the principle of adaptation.

Most striking have been the studies of Matthews (1931a, b) on the reactions of individual sensory end organs in muscle. Studying first the

frog, he was able to isolate a single muscle spindle in the small muscles of the toe and found, when the muscle was placed under slight stretch, that the spindle discharged continuously and the process of adaptation was slow. *When, however, the muscle itself was caused to contract, the responses of the muscle spindle immediately ceased* (fig. 6). He accordingly concluded that the muscle spindle lies "in parallel" with the active

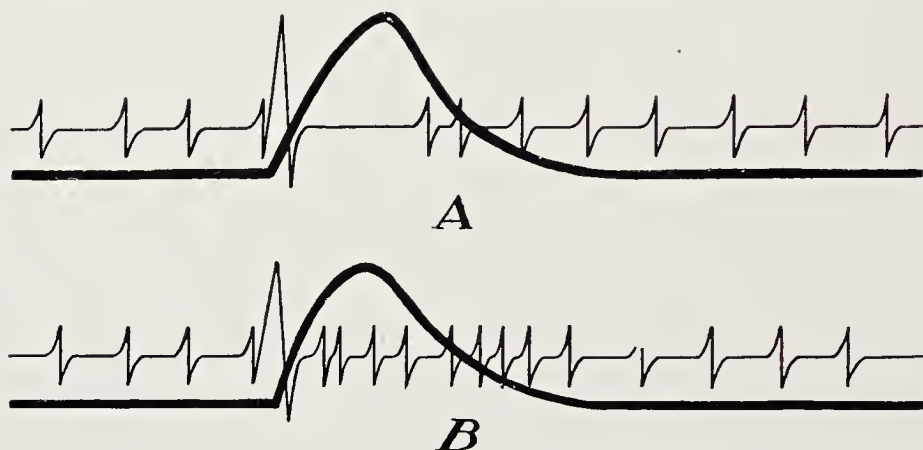


FIG. 6. Matthews' records from the nerve of a frog's toe muscle preparation, containing one muscle spindle; under 2 gm. passive stretch. Note the rapidity of discharge. A, When the motor nerve is stimulated, the muscle spindle stops discharging during the period of rising tension and commences to discharge at an increased rate when the tension falls, illustrating the response of an end organ lying "in parallel" with the tension-supporting elements (see fig. 4). B, When the motor nerve is stimulated supramaximally, the rate of discharge of the end organ's motor response is increased owing to excitation of intrafusal fibres (Matthews, B. H. C., *J. Physiol.*, 1931b, 72, 153).

fibres (fig. 5B), and that when the active fibres contract the stretch stimulus to the muscle spindle is removed. It happens that the intrafusal fibres of the muscle spindle are innervated by a small motor nerve fibre of high excitatory threshold. If this intrafusal fibre could be made to contract along with the ordinary motor fibres, the spindle should continue to discharge during the twitch of the other fibres. Matthews found his deduction to be correct for, on increasing threefold the intensity of stimulus to the motor nerve, a twitch resulted during which there was no cessation, but rather an increase in rate of discharge of the spindle.

More recently Matthews (1933) has turned his attention to the sensory endings in mammalian muscle, choosing for examination *m. soleus*, the nerve of which had been cut down to diminish the number of afferent fibres. Other muscles, especially the small muscles of the toes, were also

studied. From the mammalian muscle, Matthews has isolated four types of receptor whose discharge varies as follows with the character of the stimulus:

A₁ receptors (Flower spray endings). The A₁ receptors are stimulated by passive stretch of the muscle and, like those of the frog spindles just described, cease to discharge during active contraction. They behave, therefore, as if they lay "in parallel" with the contractile element (fig. 5B). The unstretched A₁ receptor is likely to discharge continuously at a slow rate (5 to 15 per sec.), and slight tension is prone to prolong the rate of discharge indefinitely; a quick stretch may cause these endings to discharge as rapidly as 500 per sec. When the motor nerve is stimulated supramaximally, a pause still occurs in their sensory discharge (fig. 6). Matthews has given reasons for believing that the A₁ discharge arises in the flower spray ending of the muscle spindle.

A₂ receptors (Annulospiral endings). The A₂ receptor has characteristics similar to those of A₁, except for the fact that during active contraction evoked by a supra-maximal stimulus to the motor nerve the rate of discharge of the end organs increases. As in the case of the frog spindle, this is interpreted as due to contraction of the intrafusal fibre. This converts the sensory terminal of the spindle, presumably the annulospiral ending, from an end organ lying "in parallel" with the contractile elements of the muscle into one lying "in series." The rate of conduction of impulses from the A₂ ending is more rapid than that from the A₁, which is compatible with the fact that they are innervated by a fibre of larger diameter (fig. 4, b).

B receptors (Tendon organs). The B receptors have a higher threshold than those of A₁ or A₂ and behave as if they lay "in series" with the contractile elements; that is, their response depends only upon the total tension in the muscle, whether this be the result of passive stretch or of active contraction (fig. 5A). The rate of response of these receptors is roughly proportional to the logarithm of the tension. They are therefore presumed to be the tension recorders *par excellence* and by process of exclusion Matthews attributes their response to the tendon organs of Golgi (fig. 4, g). Matthews concludes, "there are no observations that do not accord with this view."

C receptors (Fascial sheaths). Another end organ which, unlike the A and B receptors, adapts very rapidly, is sometimes encountered in muscle nerves. It generally disappears completely when the fascial coverings of the muscle are carefully dissected away. It is believed that these are possibly deep pressure endings, e.g., those from the Pacinian corpuscles.

All the histological endings known to occur in muscle have therefore been identified by Matthews, except for the pain endings in blood vessels. Matthews records that when the blood supply was cut off vigorous discharges sometimes occurred, but these were apparently from the A, B or C types of endings. It is probable that his recording method did not allow him to pick up action currents of unmyelinated pain fibres.

OTHER END ORGANS. Adrian and Zotterman (1926) have studied other isolated end organs; with some they encountered difficulties from the fact that single end organs often shared a common fibre with adjacent end organs of the same type. When there were isolated endings, the

general principles concerning variation of rate of discharge with intensity of stimulus were found in each end organ studied, *i.e.*, in muscle, pressure, touch, hair follicle and pain endings. Adaptation occurs much more rapidly in cutaneous end organs than in muscle spindles. Adrian (1932) points out that these differences in adaptation rate of end organs correspond with the different types of reflex action which they produce, *i.e.*, those underlying postural reactions which are long-sustained exhibit far less rapid adaptation than those underlying the reflexes originating in the skin (see below ch. VI and VII).

Tactile endings. Cattell and Hoagland (1931) stimulated tactile receptors in a frog's skin by the use of an interrupted air jet. They found, as had Adrian, that tactile receptors, unlike muscle receptors, adapt quickly. Their rate of discharge may be high at first, and then with mere continuation of the unaltered stimulus, diminish in rate, and finally disappear entirely. Cattell and Hoagland found that the receptors could maintain for brief intervals (0.3 sec.) frequencies as high as 250 to 300 per sec. Thereafter the end organ was no longer able to follow the rate at which it was stimulated. Incidentally, this rate of discharge is about the maximum at which a free nerve fibre can respond, so the refractory period of the end organ must be close to the refractory period of its nerve fibres.

Pain. By gradually increasing the pressure applied to a frog's skin, Adrian has been able to distinguish impulses from pain endings from those evoked by pressure. Touch and pressure are conveyed by large fibres since gentle touching of the skin gives rise to large rapidly travelling impulses. When pressure becomes more intense, trains of smaller, more slowly travelling impulses develop which are due to stimulation of the free nerve endings. For details concerning these observations see Adrian's earlier paper, (1926) his monograph (1932) and the recent work of Echlin and Propper (1937).

SUMMARY

Receptors are specialized cells which have developed to respond to particular changes in the environment. These changes vary widely in character, embracing heat, cold, light, sound, mechanical deformation, chemical change, etc. In higher animals the receptor affected by environmental change communicates with the central nervous system by an afferent nerve fibre which passes to the brain or spinal cord *via*

ganglion cells lying, in the case of the spinal cord, along dorsal nerve roots.

There are two primary groups of afferent end organs: (i) the exteroceptors and (ii) the interoceptors. The *exteroceptors* include all those end organs affected by the external environment, *i.e.*, the special senses of vision, hearing (distance receptors), taste, smell (chemical receptors), and the cutaneous receptors. The *interoceptors* are divided into two groups: (i) the proprioceptors (muscle and labyrinth) and (ii) the visceroreceptors (gut, heart, blood vessels, bladder, etc.).

The cutaneous exteroceptors are made up of free nerve endings and plexuses which often terminate in multiple loops one above the other and independently innervated, and more highly organized corpuscles which, according to Weddell's latest evidence, probably subserve special sensory modalities as follows: Merkel's and Meissner's corpuscle and hair cells (tactile sensibility), Krause's end bulbs (cold), Ruffini's (warmth) and Golgi-Mazzoni's corpuscles (pressure).

The proprioceptors include the muscle spindles (stretch afferents), Golgi tendon organs (tension recorders), Pacinian corpuscles (deep pressure), and free nerve endings (pain). The visceroreceptors also include Pacinian corpuscles, pressure recorders in blood vessels, and a wide variety of free nerve endings (pain).

All receptors transmit messages to the central nervous system by means of all-or-nothing nerve impulses. The only way in which the intensity of a stimulus can be conveyed to the nervous system is through change in rate and total duration of discharge of the end organs, or through the stimulation of additional end organs of the same type. Intensity is thus registered by means of spatial and temporal summation of impulses.

Any end organ subjected over a period of time to a constant stimulus manifests a diminishing rate of discharge. This phenomenon is known as "adaptation" and is of wide significance in the analysis of sensory processes. Muscle receptors adapt slowly, whereas touch and pressure end organs adapt with great rapidity.

Muscle receptors are of two principal types: those lying "in parallel" with the active constituents (muscle spindles), which signal increase in passive tension — hence "stretch afferents" — and those "in series" with the contractile fibres (tendon endings), which react to tension irrespective of whether it is active or passive — hence "tension recorders."

II

DORSAL SPINAL NERVE ROOTS AND THE DERMATOMES

HISTORICAL NOTE

The sensory function of the dorsal spinal nerve roots was unequivocally established in 1822 by the experiments of François Magendie. It is true that the separate existence of sensory and motor nerves had been postulated by Galen, Kenelm Digby, Descartes, Robert Whytt and others, but prior to Magendie the motor and sensory functions of the dorsal and ventral nerve roots had not been established experimentally. In 1809 Alexander Walker had suggested that the spinal roots subserved separate functions, but unfortunately he concluded that the ventral roots were sensory and the dorsal roots motor. Charles Bell, whose name is closely linked with that of Magendie, had issued in 1811 a privately printed pamphlet entitled *Idea of a new anatomy of the brain*, in which the motor function of the ventral nerve roots was recognized; the sensory function of the dorsal roots, however, was not established by Bell in this or in his subsequent writings, and his "proof" of the motor functions of the ventral root left much to be desired. "On laying bare the roots of the spinal nerve," he said, "I found that I could cut across the posterior fasciculus of nerves which took its origin from the posterior portion of the spinal marrow without convulsing the muscles of the back; but that on touching the anterior fasciculus with the point of a knife the muscles of the back were immediately convulsed." In turning to the experiments of Magendie one steps from the misty clouds of uncertainty into the warm sunshine of well conceived experiment. To quote his protocol (1822, p. 277), "I then had a complete view of the dorsal roots of the lumbar and sacral pairs, and on lifting them up successively with the points of a small pair of scissors, I was able to cut them on one side . . . I then observed the animal. I at first thought the member corresponding to the cut nerves was entirely paralyzed; it was insensible to the strongest prickings and pressures, and it seemed to me also incapable of moving; but soon, to my great surprise, I saw it move in a manner very apparent, although sensibility was entirely extinct. A second and third experiment gave me the same result; I began to think it probable that the dorsal roots of the spinal nerves might have different functions from the ventral roots, and that they were more particularly destined for sensation" (p. 261). Magendie also established unequivocally the motor functions of the ventral roots. The priority of both discoveries was questioned by Bell, but a survey of the documentary evidence makes it clear that Magendie, and not Bell, deserves unqualified credit for the discovery of the sensory function of the dorsal roots. Magendie, however, *did not suggest that this was their only function*.

Anatomical analysis of the dorsal root complex lagged considerably behind physiological study. Indeed, the site of termination of all dorsal root fibres is not yet known. It was the Norwegian explorer Nansen (1886) who first pointed out

that each dorsal root fibre divides, on entering the cord, into an ascending and a descending branch, both of which give off numerous collaterals in various segments of the spinal cord (fig. 7). Recognition of the importance of the unmyelinated fibres in the dorsal roots is due largely to Ranson (1912) whose untimely death in 1942 we are now obliged to record.

THE central nervous system is kept in touch with the external and internal environment of the body by means of impulses which traverse the dorsal spinal nerve roots into sensory pathways of the suprasegmental divisions of the nervous system. The present discussion will be limited to the spinal segments, where the sensory roots can be readily isolated for study. It is essential first to outline the anatomical constitution and

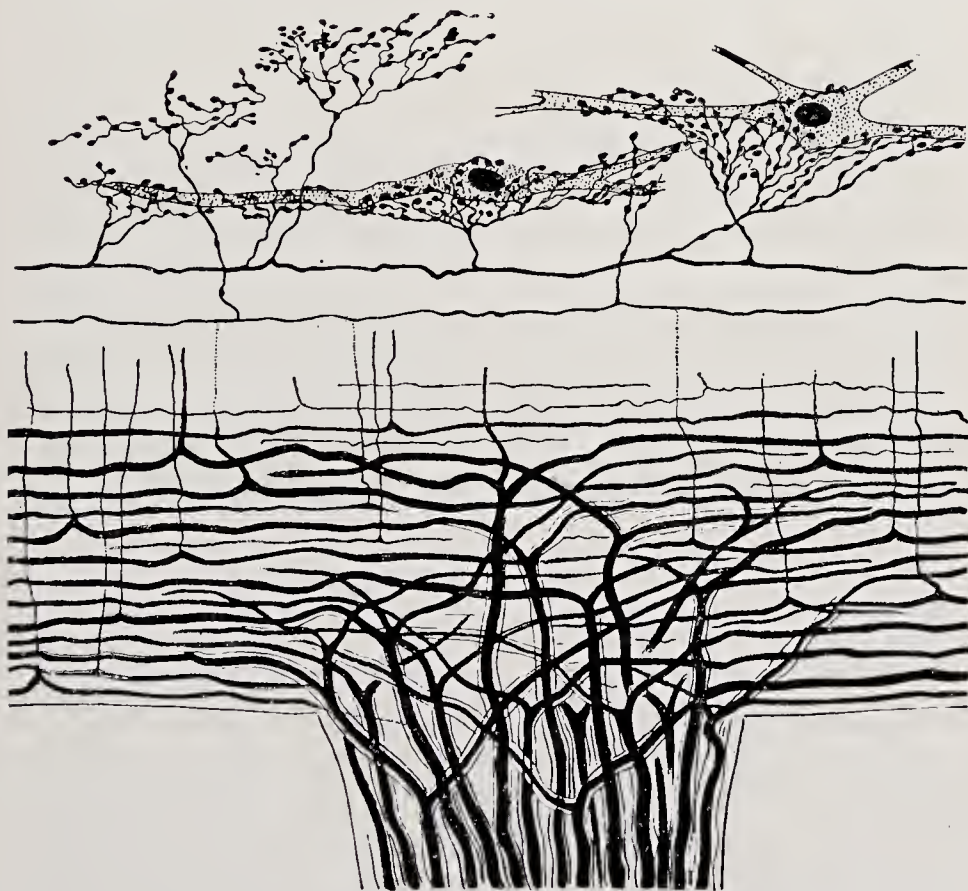


FIG. 7. Drawing of the bifurcation and ramification of fibres from dorsal rootlet entering spinal cord. Below a rootlet with many fibres all bifurcating on entry, and subsequently giving off collaterals. Above two fibres ending in characteristic boutons terminaux upon two cells of origin of spinothalamic tract (from silver impregnations of Ramón y Cajal combined by Edinger, *Vorlesungen über den Bau der nervösen Zentralorgane*, Leipzig, 1911, p. 142).

terminations of the dorsal root fibres, and then the principal categories of function will be described.

ANATOMICAL DETAILS

The dorsal spinal nerve roots extend from the first cervical to the lowermost sacral segments of the spinal cord. The number of dorsal roots varies in different animals, and in any given species there are individual variations; the spider monkey, for example, has a large number of additional sacral and coccygeal segments innervating its prehensile tail, whereas the three-toed sloth *Bradypus* has two additional cervical roots (the giraffe, oddly enough, has the usual number, but the rhesus monkey lacks the first cervical roots, Zuckerman, 1938). In man there are generally 8 cervical, 12 thoracic, 5 lumbar and 5 sacral segments, making a total of 30 dorsal nerve roots on each side. Each root is composed of myelinated and unmyelinated nerve fibres, the myelinated fibres having a wide range of diameter from 1 to some 20 *microns* (see fig. 8). The unmyelinated fibres constitute at least 40 per cent by number of the total roots, being greater in the thoracic and sacral regions than in the cervical and lumbar, (Davenport *et al.*, 1931, 1934, 1937) a fact which has been correlated with special innervation of the extremities.

The ratio of the number of *myelinated* fibres in a dorsal root proximal to the ganglion to the total number of cells in the ganglion varies from 1 to 2.5 to 1 to 3.2; when only the large cells are considered, the ratio is about 1 to 1 (Ranson, 1911). When unmyelinated fibres are also counted, the ratio of *total* cells to fibres also approaches 1 to 1; early reports suggested that there were more ganglion cells than countable fibres proximal to the root (Barnes and Davenport, 1937). In dorsal roots of cats, however, Duncan and Keyser (1936) found in their best preparations that the number of fibres slightly exceeded (never more than 10 per cent) the number of cells in the ganglia. Later both Duncan and Keyser (1938) and Holmes and Davenport (1940), after examining all roots from C1 to Cc4 (lowest coccygeal) of the cat, conclude that a 1:1 ratio exists between cells and fibres. The total number of dorsal root fibres averaged 535,000 one side (all segments), while the total for the ventral roots was 115,000, the ratio of dorsal to ventral root fibres thus being of the order of 1:4.65. The total number of myelinated fibres in the 8th and 9th thoracic roots of human beings is said to decrease with age (Corbin and Gardiner, 1937).

Before reaching the spinal cord the dorsal roots break up into a series of filaments which spread fanlike in the intradural spaces to enter the dorsal horn at the dorsolateral sulcus. They form an uninterrupted line from the first cervical to the lowermost sacral segments of the cord. Just before entering the cord, the individual *filaments* separate into two parts:

(i) a medial division made up principally of myelinated fibres which pass over the tip of the dorsal horn to enter the dorsal columns (of Goll and Burdach); (ii) a smaller lateral division composed principally of unmyelinated and small myelinated fibres which actually enter the tip of the dorsal horn of spinal grey matter. As already indicated, each fibre on reaching the cord divides into an ascending and a descending branch

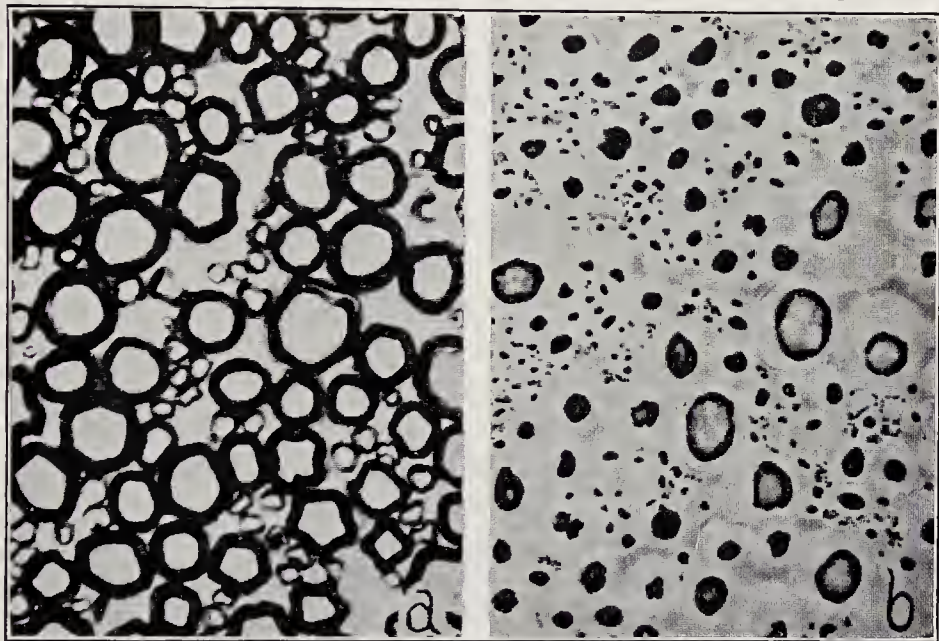


FIG. 8. Cross sections of dorsal spinal nerve roots at third sacral level (dog). On left osmic acid staining showing the medullated fibres. On right silver stains showing axis cylinders of both medullated and unmedullated fibres. *a*, Dorsal root, osmic acid stain $\times 1000$. *b*, The same root, silver stain $\times 1400$ (Davenport and Ranson, *Amer. J. Anat.*, 1931, 49, Plate I).

(fig. 7), and silver preparation demonstrates that each division sends numerous collaterals as shown in Waldeyer's classical figure of branching dorsal root fibres (fig. 9). The larger fibres among the ascending branches make up the dorsal columns of Goll and Burdach, and, though they too send off numerous collaterals, they do not terminate until they reach the medulla.

The site of termination of the dorsal root fibres has been studied by the Marchi technique, which is useful for tracing tracts, but does not allow exact determination of their ending; the stains for degenerating boutons allow one to determine on what cell a degenerating axon ends (see ch. iv) and thus give more precise information concerning the des-

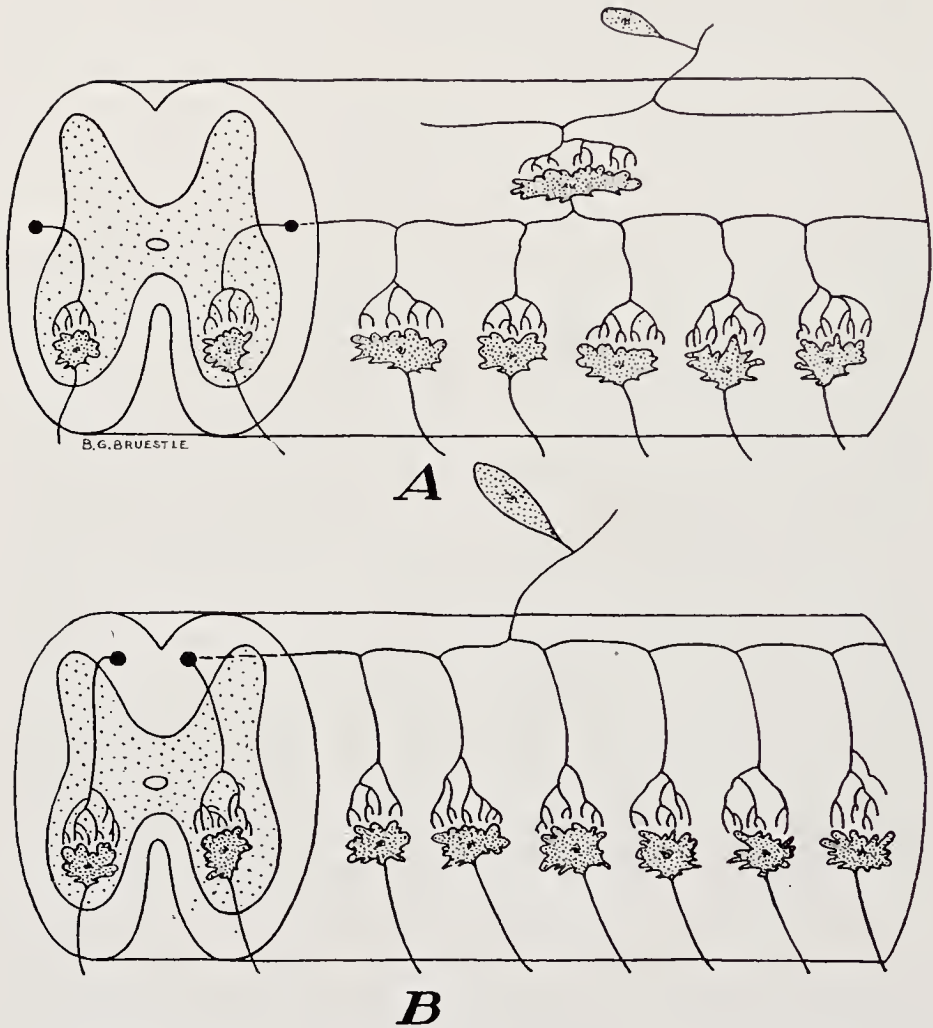


FIG. 9. Two diagrams showing ramification of single dorsal root neuron in spinal cord. A, Bifurcation and termination of collateral upon internuncial neuron, which in turn communicates with 6 ventral horn cells. B, Another and larger dorsal root neuron passing in dorsal column and sending collaterals directly to 6 ventral horn cells (redrawn from Waldeyer's paper on neuron doctrine, 1891, p. 25).

termination of the fibres.* Six primary regions of termination have been recognized as follows:

* Although Rasdolsky (1923) and others had described bouton degeneration, the first to study degenerating boutons for ascertaining the site of termination of fibre pathways in the central nervous system was E. C. Hoff (1932a&b, 1933, 1935, 1937; Hoff and Hoff, 1934). Foerster, Gagel and Sheehan (1933) employed the method for tracing the termination of dorsal root fibres in the spinal cord, and the Russian histologist Lawrentjew (1924, 1934) employed the bouton technique for tracing autonomic degenerations. Although the validity of the method has been questioned, the results of Hoff, Foerster, *et al.*, have been substantially confirmed by Gibson (1937a&b). (See also Barr, 1939 and ch. iv.)

(i) *Ventral horn cells.* In adult animals a few fibres pass directly to the cells of the ventral horn (cat and monkey), their proportion varying at different levels, a larger number being found in the lumbar and lower cervical segments. In the early silver impregnations of Cajal (see Waldeyer, 1891) it was shown that many of these direct fibres are collaterals from dorsal column fibres (fig. 9B). The existence of such direct fibres has been thoroughly substantiated by the bouton de-generation technique (ch. III).

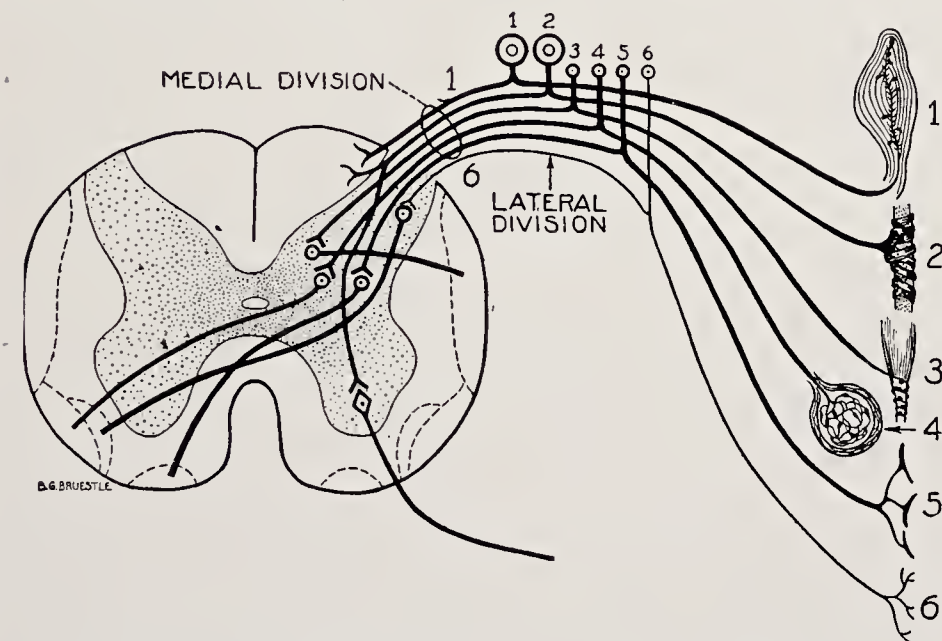


FIG. 10. Diagrammatic cross section of spinal cord showing principal sites of termination of dorsal root fibres. 1 and 2 represent large medullated fibres having large dorsal root ganglion cells and passing to the dorsal columns; they arise from Pacinian (1) and muscle spindle endings (2). 3 and 4 terminate on dorsal horn cells that cross and give rise to spinothalamic and spinocerebellar tracts. 5, a similar cell terminating on neuron that gives rise to ventral spinothalamic tract. 6, a small fibred neuron (pain) terminating in substantia gelatinosa of Rolando giving rise to fibre of ascending spinothalamic tract of opposite side.

(ii) *Intermediate grey.* The majority of dorsal root fibres which actually enter the dorsal horn terminate upon internuncial neurons in the intermediate grey matter of the cord; in the thoracic levels, however, none appear to terminate upon the cells of the lateral horns (Foerster, *et al.*, 1933). As yet no clear difference in fibre composition has been established between those which pass to the intermediate grey and those passing to the other regions of the cord.

(iii) *Clarke-Stilling column.* The Clarke column cells are said to be limited to the thoracic and upper two lumbar segments, which fact led Gaskell (1885) to associate them with the sympathetic nervous system. As Sheehan points out (1935), however, there are in the cervical and sacral regions the correspondingly situated nuclei of Stilling. From both Stilling's and Clarke's column cells, neurons arise which pass into the dorsal spinocerebellar tract of the same side (fig. 10), carrying impulses from the limb musculature to the ipsilateral nuclei of the cerebellum. A

few dorsal root fibres pass directly to the Clarke's column cells of the opposite side(Foerster).

(iv)*Dorsal horn cells.* The neurons in the dorsal horns also receive posterior root fibres, and in turn give rise to the ventral spinocerebellar tract fibres passing both to the same and to the opposite side; it carries proprioceptive impulses from the trunk musculature.

(v)*Substantia gelatinosa.* Other dorsal root fibres terminate in the substantia gelatinosa of Rolando. From here secondary neurons arise which pass by the ventral commissure to form the spinothalamic tracts in the opposite ventrolateral columns(fig. 10). Some posterior root fibres may cross directly and terminate on internuncial neurons on the opposite side. These crossed fibres convey pain, heat and cold; from Foerster's(1927)observations on cordotomy it is clear that they cross within one or two segments of their point of entry into the spinal cord. Fibres conveying tactile sensibility are believed to pass up the cord in the dorsal horn for several segments before crossing to the opposite side where they form the ventral spinothalamic tract.

(vi)*Gracilis and cuneate nuclei.* The branches of the dorsal root fibres which pass upward in the dorsal columns have their first synaptic connections with suprasegmental centres in the nuclei of Goll and Burdach which lie in the posterior part of the medulla. These ascending fibres give off many collaterals to internuncial neurons(fig. 9)and to anterior horn cells lying in the spinal grey matter, and are believed to underlie such intersegmental reactions as the scratch reflex(ch. vi).

SENSORY FUNCTIONS

The several modalities of sensation mentioned in the first chapter are subserved by discrete fibres which have varying destinations in the spinal cord and medulla. It is as yet impossible to infer from the physical characteristics of the fibre the character of the sense modality which it subserves. However, it is well established that the larger sensory fibres are concerned with the more highly organized end organs, and hence with the more recently acquired sense modalities such as touch, pressure and proprioceptive sensibility; thus the Pacinian corpuscles are generally connected with fibres of the group ranging from 15 to 18 *microns* in diameter, and the largest fibres of 18 *microns* or above come from sensory end organs in muscles, presumably the annulospiral endings of the spindles. Recognition of pain fibres has an interesting history which may be described in greater detail.

PAIN PATHWAY.* In 1912 Ranson published the first of a series of papers in which it was argued that the unmyelinated fibres of the dorsal roots conduct pain sensibility. Sheehan(1935)has summarized his evidence as follows:

* Rivers' and Head's(1908)earlier work on "epicritic" and "protopathic" sensibility of the skin presupposed that the unmyelinated sensory fibres subserved pain. For further details Lewis'(1942)monograph on pain should be consulted.

(i) Unmyelinated fibres of the lateral division of the root filaments terminate almost immediately on entry into the cord, after a short course of one or two segments in the tract of Lissauer. This corresponds closely to the known course of "pain impulses" as deduced from clinical studies.

(ii) Unmyelinated fibres are found chiefly in the cutaneous nerves. The greater sensibility of the skin than of the deeper structures to painful stimuli is a well-recognized surgical observation. Furthermore, the unmyelinated fibres are present in much greater numbers in such nerves as the lateral cutaneous of the thigh, whose areas of distribution show a greater sensibility to painful than to tactile stimuli.

(iii) Unmyelinated fibres are the earliest to appear phylogenetically. Pain is phylogenetically the most primitive sensation.

(iv) Experimental section of the lateral division of the root filament of the seventh lumbar dorsal root in the cat, without injury to the medial division, at once eliminated the pain reflexes (*e.g.*, struggling, changes in respiration, and rise in blood pressure) obtainable from this root in the anesthetized animal.

The evidence was impressive, but it did not indicate whether other fibres, *e.g.*, the small myelinated group, might also conduct pain. Thus the fifth cranial nerve has few unmyelinated fibres and yet pain sensibility of a fairly discrete character is obviously associated with the fifth nerve. With the application of the cathode ray oscillograph, further evidence was forthcoming. As is now well known, the action currents in mixed nerves fall into three groups: the A, B and C waves (Erlanger and Gasser, 1930). The A fibres are rapid and correspond with the larger motor and sensory medullated fibres. The B waves are considerably slower and have been associated with the more finely medullated fibres, whereas the slowest C waves have been shown to arise in unmyelinated fibres, partly from the sympathetic, partly from other sources, and these studies also indicated that some of the C group were afferent.* Clark, Hughes and Gasser (1935), in studying the effects of asphyxia on the modalities of sensation, *give conclusive evidence that localizable pain is associated with the small medullated fibres of the B group*, and while diffuse unlocalized pain, which persists for 45 minutes after circulation is cut off, is associated with the C group, some degree of localization is possible even when the C group alone is active. This group is capable of inducing reflex effects on blood pressure and respiration in cats when the A and B groups have dropped out as a result of 45 minutes of asphyxia. In man warmth and unlocalized pain are the only exterocep-

* There have been many recent papers on the C fibres; attention may be directed especially to those of Heinbecker, O'Leary and Bishop (1933), Tower (1933) and to Grundfest and Gasser (1938). B fibres are made up largely of preganglionic axons.

tive cutaneous modalities which remain after a corresponding period of complete asphyxia (Lewis, 1942).

Nerve-trunk anesthesia. The small diameter of the slow pain fibres and their relative absence of sheath makes them more vulnerable to chemical agents, especially local anesthetics (and also to increased concentrations of potassium), than are the large myelinated fibres. It is therefore possible to abolish conduction of the C fibres, *e.g.*, with novocaine or K, while conduction of the A and B group (and hence of touch, pressure and thermal sensibility) remain functional. This is of immediate practical significance as far as "block" anesthesia of nerve trunks is concerned, since it makes possible diminution or abolition of pain, leaving touch and position sensibility virtually unaffected. Pressure, on the other hand, applied to a mixed nerve trunk affects first the fibres of larger diameter since they are more subject to distortion (as well as to lack of oxygen), than are the smaller fibres.

Dual pain systems in skin. In addition to the dissociation demonstrable between pain and tactile sensibility in block anesthesia of a nerve trunk, it is also possible to demonstrate dissociation in the mechanisms of pain sensibility itself. Thus, Gasser (1935) found that asphyxia knocked out localizable pain in the skin, while the diffuse, slow-responding pain sensibility still remained. He concluded on the basis of action current studies that the quick-acting pain receptors were subserved by small medullated fibres, whereas the second, slow-acting pain modality was mediated by small, unmedullated fibres of the C group. Lewis and Pochin (see Lewis, 1942) have studied the dual pain mechanism in skin, finding that the two can be readily separated in intact human skin by the use of a special heated cylinder applied at 60 to 65° F. Brief contact of this instrument with the skin gives an immediate sting (rapid component) which, after contact is broken, is followed by an "echo" — a flash of pain of greater intensity. If the two pain modalities are conducted to the brain at different rates, the perception interval for the second modality should increase relatively as the distance from the sensorium is increased. This they found to be the case, for the "echo" at the toe was appreciated in 1.9 seconds, at the knee 1.3, and at the top of the thigh 0.9 seconds.

Interruption of pain pathways in spinal cord. Section of the lateral root filaments of the dorsal roots for relief of pain is technically difficult, but since the pain fibres, on entering the spinal cord, cross and pass upward toward the thalamus in the ventro-lateral columns, Foerster (1927b) and others have found that intractable pain may be effectively relieved in man by a "cordotomy" — *i.e.*, surgical section of the ventro-lateral columns on the side opposite to the source of the pain.

VISCERAL AFFERENTS. The receptors responsible for sensibility of the abdominal and other viscera are related to those subserving pain elsewhere in the body. As pointed out in chapter 1, there are highly organized Pacinian corpuscles in the mesentery, obviously sensory in function, and in addition there are large numbers of more primitive sensory endings conveying pain. Langley (1903) sectioned the dorsal root distal to its ganglion and found that virtually all of the medullated fibres in the corresponding white rami communicantes had degenerated (ch. XII).

Section of the sympathetic trunk or the splanchnic nerve did not cause such degeneration. On the basis of these observations, Langley concluded that the majority of visceral afferent fibres were of the small medullated group. These studies shed no light upon the possible existence of unmedullated sensory fibres. For a review of the problem see the papers of Hinsey(1934)and of Sheehan(1935).

Cell station of visceral afferents. Injury to the sympathetic trunk or the white rami is followed by retrograde degeneration of as many as 5 per cent of the cells in the corresponding posterior root ganglia(Warrington and Griffith, 1904). The problem was taken up anew by Sheehan, who found that the living Pacinian corpuscle in the mesentery could be readily stained by methylene blue. Section of the vagi below the diaphragm did not cause degeneration of the nerve fibres in the corpuscles, whereas if the splanchnics were severed on both sides the nerve endings degenerated and in addition chromatolysis could be demonstrated in appropriate dorsal root ganglia. From this it was concluded that visceral afferent fibres passed from their Pacinian corpuscles into the splanchnic nerve and thence directly to the spinal cord via the dorsal roots. If, however, the dorsal roots were severed proximal to the ganglia, no degeneration occurred in the Pacinian corpuscles, since in those circumstances their cell bodies remained intact; when severed distal to the ganglia, the nerve ending degenerated. It was thus obvious that these highly organized endings have their cell stations, like other sensory fibres, in the posterior root ganglia. The study gave no evidence, however, whether *all* visceral afferents pass to the cord in this way.

From time to time, various authors have suggested(see Sheehan, 1935)that some visceral afferents have their cell stations in the sympathetic ganglia. Kuntz (1913) has adduced evidence of local sympathetic reflexes which do not involve the spinal cord at all. He conceived of the autonomic nervous system as a collection of reflex arcs involving both afferent and efferent fibres, some of which were strictly local with cell stations in the walls of the particular organs innervated. Schwartz(1934)further supported the concept of extraspinal sympathetic reflexes by cutting the dorsal roots of the entire upper limb *distal* to the dorsal root ganglia. After time had elapsed for degeneration, he was still able to obtain "galvanic reflexes" from the skin; nicotine abolished the reaction, which suggests true synaptic transmission quite separate from an axon reflex(cf. Uprus, *et al.*, 1935). Leriche(1937)in his recent monograph on the surgery of pain lays great stress upon such local reflexes.

POSSIBLE EFFERENT FUNCTIONS

In 1876 Stricker observed that stimulation of the distal end of a divided dorsal lumbar root caused a rise in temperature of the footpads in dogs. The response was evidently due to peripheral vasodilatation. Similar observations were made by Werziloff(1896), who also observed a fall in skin temperature on section of the dorsal roots. He found in addition that the blood pressure fell when the dorsal roots were thus stimulated

distally. Using a plethysmograph, Bayliss(1901)confirmed the observation and the phenomenon has been fully studied in man by Foerster (1925, 1928). On the basis of these observations various writers, including Bayliss and Foerster, have postulated the existence within the dorsal roots either of antidromic conduction(Bayliss, 1901)or of efferent vasomotor fibres(Foerster, Lewis, etc.), but, prior to Toennies'(1938, 1939)papers (see p. 34), there had been little evidence of the existence of such dorsal root outflow in the normal animal.

Bayliss found that the depressor reflex from stimulation of the central end of the vagus nerve was still obtainable after complete removal of the sympathetic supply to the part studied. Zuckerman and Ruch(1934)noted that the fully denervated limb in monkeys reacted to changes in environmental temperature in a manner different from the limb in which the dorsal roots remained intact. When still possessed of sensory innervation, the skin temperature sometimes fell with reflex suddenness; the problem is clearly one which requires further study.

The general interpretation of the results of Bayliss has been that sensory fibres exist in the dorsal roots which, in addition to subserving sensory functions, also, perhaps by dichotomy, innervate the arterioles, thus forming the anatomical basis of the axon reflex. This general explanation was supported by the work of Lewis (1927)on the triple response in which the "flare" was attributed to dichotomizing sensory fibres which presumably subserve pain. More recently, however, Lewis(1942)has postulated the existence of a separate "nocifensor" system of nerves, having origin in the dorsal roots and being efferent rather than afferent in function(see below, p. 34).

Efferent fibres of dorsal roots. It is still generally believed that many of the unmyelinated fibres in dorsal roots, and part of the small myelinated group have not yet been adequately accounted for anatomically or physiologically. Thus many observers have found intact axis cylinders in the central ends of the divided dorsal root after sufficient time has elapsed for degeneration of the afferent fibres whose cells of origin lie distally in the spinal ganglia.* The number of axis cylinders in the central trunk differs widely from one level to the next and in different animals. The early details of the controversy are reviewed by Hinsey(1934)and Sheehan(1935). Young and Zuckerman(1937), using osmic acid staining, have found small myelinated fibres in the proximal ends of cut dorsal roots of monkeys, especially in the lumbar outflow. Story, Corbin and Hinsey(1936), however, have been unable to find degenerating fibres in the dorsal roots of cats *distal* to the section of the root, and the 1:1

* Efferent dorsal root fibres have been described by many authors, especially Kahr and Sheehan(1933)in cats, Okelberry(1935)in dogs, and Young and Zuckerman(1937)in macaques.

ratio now established between ganglion cells and dorsal root fibres is strong evidence against the existence of true dorsal root efferents (see above, p. 24).

All who have investigated the problem, including Hinsey and Tower, find intact axis-cylinders in the proximal end of divided dorsal roots after intervals of 12 to 25 days when afferent fibres would have degenerated, but Hinsey and Tower both maintain that these are *regenerating* fibres. However, they are present, even in preparations from which the dorsal root ganglia have been removed in cat, dog and monkey. The fact that the fibres are present after ganglionectomy and at intervals of 12 to 15 days after the operation suggests, but clearly does not prove, that they are efferent fibres, and not regenerated fibres from an unknown source (*e.g.*, ventral root fibres degenerating back into the cut dorsal root). The work of Barron and Matthews (1935) and of Young and Zuckerman (1937) suggested at first that these degenerated fibres are, in part at least, collaterals from adjacent dorsal roots, and being collaterals, that their cell bodies lay in an adjacent dorsal root ganglion. A further point emphasized by Sheehan (1935) is that antidromic conduction across the synapse at the central end of the dorsal root fibre would defy the principle of forward conduction in the nervous system; whereas the presence of an efferent system such as the nocifensor system postulated by Lewis (1942) does not conflict with the idea of forward conduction. Toennies (1938) found that a profuse *centrifugal* discharge occurs in the central ends of cut sensory nerves (*e.g.*, a cat's internal saphenous), corresponding with the onset of certain reflexes such as the homolateral flexion reflex induced by a single break shock stimulus. The impulses emerge from the spinal cord *via* the dorsal roots after a latency of 3.5–4.5 msec. in the ipsilateral reflex and after 4.2–6.5 msec. in the contralateral reflex. This efferent discharge involves the fastest fibres (conducting at 80 m. per sec.), as well as a discrete group of slower fibres of delta velocity. The discharge shows spatial summation (ch. iv), and other characteristics of ventral root reflexes, *e.g.*, it is promptly abolished by asphyxia. Toennies did not ascertain whether the impulses traverse true dorsal root efferents or merely sensory fibres which conduct antidromically. The discharge is increased by a fall of temperature of the cord (Barron and Matthews, 1939; Toennies, 1939).

Toennies' antidromic discharges have proved more complex than was first anticipated. Barron and Matthews' "recurrent discharge" over dorsal roots can no longer be implicated since the rootlets carrying such discharge displayed no sign of degeneration in their distal portions after section (Barron and Matthews, 1940). Severance of the dorsal columns above the active rootlets put an end to the discharge. Hursh (1940), also working in Gasser's laboratory, found that the Toennies antidromic discharge was associated with a simultaneous transmission of impulses up the dorsal columns, evidently along the ascending branches of the active dorsal root fibers. Renshaw and Therman (1941) find that impulses ascending in the dorsal columns "condition" adjacent inactive fibers to stimulation, especially if the dorsal columns have been interrupted rostral to the segments being studied. Similar subthreshold changes in excitability of medullated axons in frog nerve have been described by Erlanger and Blair (1940), and the disclosures suggest that the dorsal root discharge of Toennies, as well as that of Barron and Matthews, although of great theoretical interest in connection with the excitability of more complex fiber systems, probably plays little part in the general physiology of the spinal cord (see Anderson, Livingston and Dow, 1941).

DERMATOMES IN MAN

The sensory levels of the nervous system, more than any other part of the organism, preserve the original embryological division of the body into metameters. The segments innervated by each pair of dorsal nerve roots constitute the metamere, and the skin area supplied by these sen-

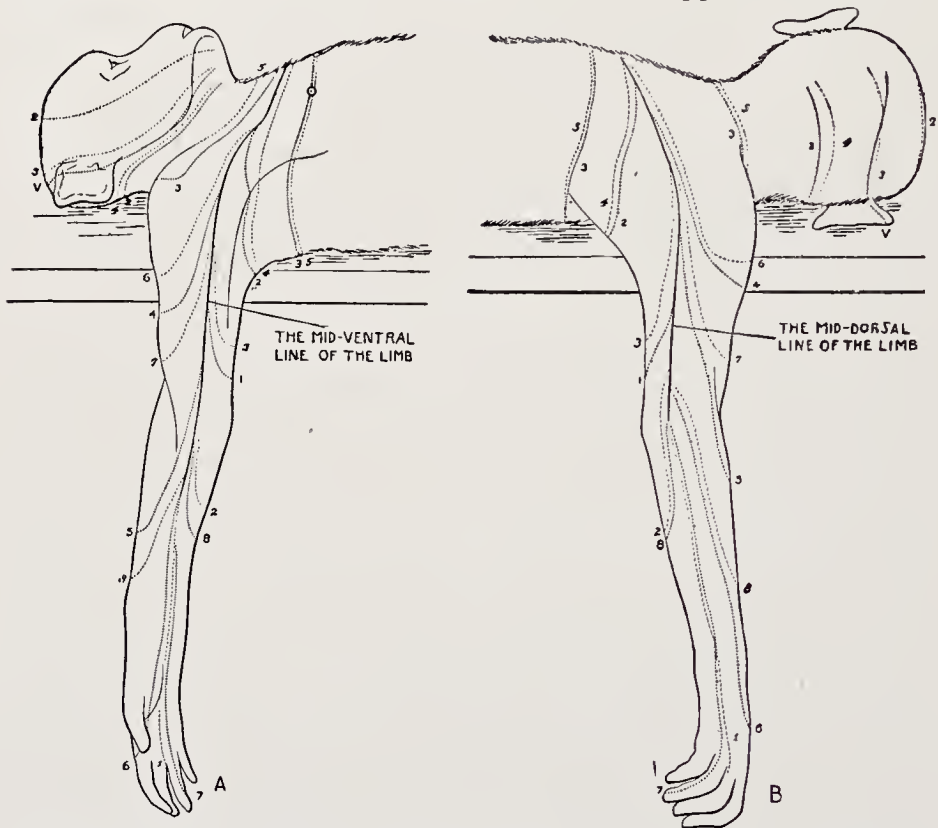


FIG. 11. Dermatomes of macaque determined by method of "remaining sensibility" (Sherrington, 1898). A, Dermatomes of upper extremity and neck; cervical 1 to 8, thoracic 1 to 5. Ventral view. B, The same, dorsal view.

sory fibres is referred to as a "dermatome." The ventral roots also innervate the dermatomes and the correspondence between the motor and sensory distribution is often close, especially for the sudomotor, pilomotor and vasoconstrictor fibres, but they never exactly coincide. The sensory dermatome corresponds more closely with the vasomotor, sudomotor, etc. than does the motor dermatome, especially as regards overlapping. The boundaries of the dermatomes are difficult to ascertain in the intact human being. They have been investigated by anatomical and

physiological methods. The anatomical method of simple dissection is fraught with difficulties because the ultimate ramifications of a given dorsal root are not easy to follow and the fibres themselves are often lost as they intermingle in the larger plexuses.

The physiological method of determining the "remaining sensibility" was introduced by Sherrington (1893b, 1898a). The method consisted in severing three consecutive dorsal nerve roots of monkeys above and three below a single root which is allowed to remain intact. The area of skin retaining sensibility after this root section represents the full extent of the sensory dermatome of the intact root. Another physiological method lies in local strychninization over a single dorsal root segment. In these circumstances the circumscribed area of skin develops hyperesthesia (Dusser de Barenne, 1910). Both methods have indicated extensive overlapping of individual dermatomes. Indeed, a law has been enunciated, attributed to Sherrington, which states that on account of overlapping of individual root areas at least three contiguous roots must be severed on each side of the root whose dermatomal distribution is to be studied.

Foerster (1933, 1936) has also used a third physiological method for defining dermatomes applicable to man and based on the "antidromic" response of Stricker and Bayliss. The vasodilatation which follows stimulation of the distal cut end of a dorsal root is limited in extent to the dermatome as outlined for the same root by the isolation method, but is generally considerably less broad. It approximates rather with the somewhat more restricted area of dermatomal distribution defined by Head (1920) in man on the basis of herpetic eruptions (fig. 12A).

For the extent of each of the human dermatomes Foerster's final and profusely illustrated account in the *Handbuch der Neurologie* (1936) should be consulted. The dermatomes correspond in general distribution with those determined by Sherrington in the macaque (fig. 11). Foerster, in the course of a long experience with dorsal root sections, had opportunity of defining nearly every dermatome of man by the method of remaining sensibility (fig. 12B); in order to diminish pain from a given region of the body some surgeons had cut alternate dorsal roots so as to diminish the total number of pain fibres. Foerster found it more effective, and no more harmful to the human being, if three roots were cut above and below a given region of pain, leaving a central root intact. This unique opportunity for establishment of dermatomal distribution

in man has led Foerster to give the first map of human dermatomes to be based upon direct determination. His scheme of the lumbar, thoracic and cervical dermatomes is given in figure 12B.

ABERRATIONS OF SENSIBILITY (ERYTHRALGIA, HYPERALGESIA). Lewis and his colleagues at the University College in London have, during the

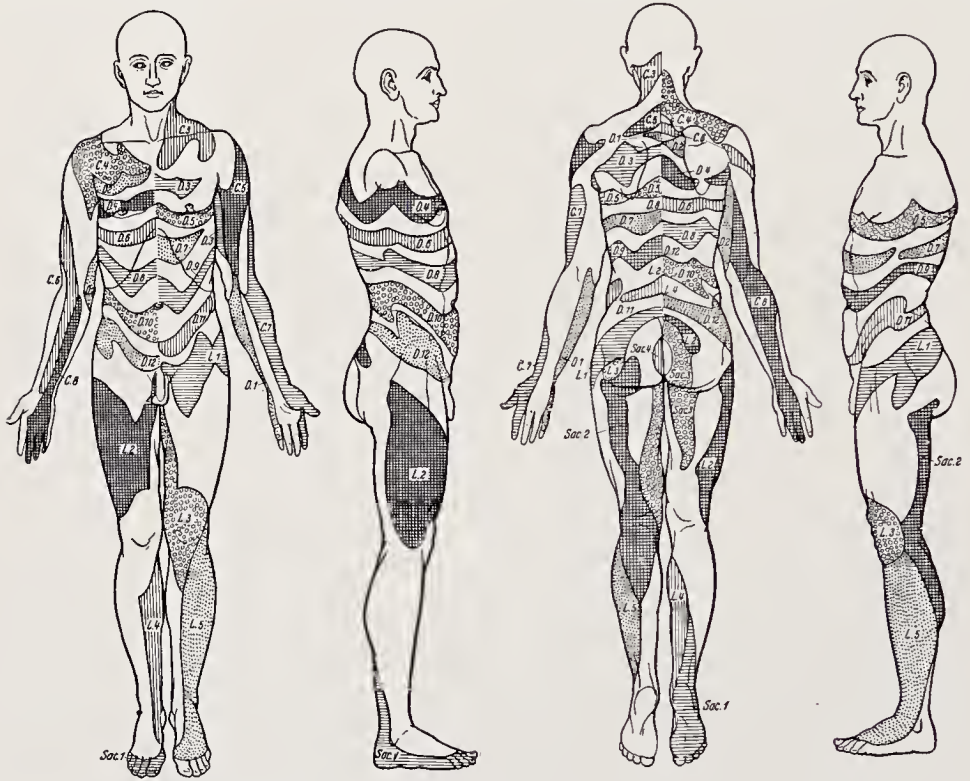


FIG. 12A. Human dermatomes as worked out by Head(1920)on the basis of herpetic eruptions in man.

past ten years, made a detailed study of the aberrations of cutaneous sensibility associated with vasomotor disturbance, asphyxia, frost bite, and mechanical injuries to the skin. Following a closely reasoned argument Lewis(1942ab&c)has developed a new concept of pain sensibility and its deviations which may be summarized briefly as follows: Injury to the skin, whether it arises from freezing, exposure to actinic light or from direct mechanical trauma, brings on a state of hypersensitivity common to all forms of injury, differing from one another in degree, but not in basic mechanism. Cutaneous injury is associated with the liberation of a chemical substance which, diffusing through the tis-

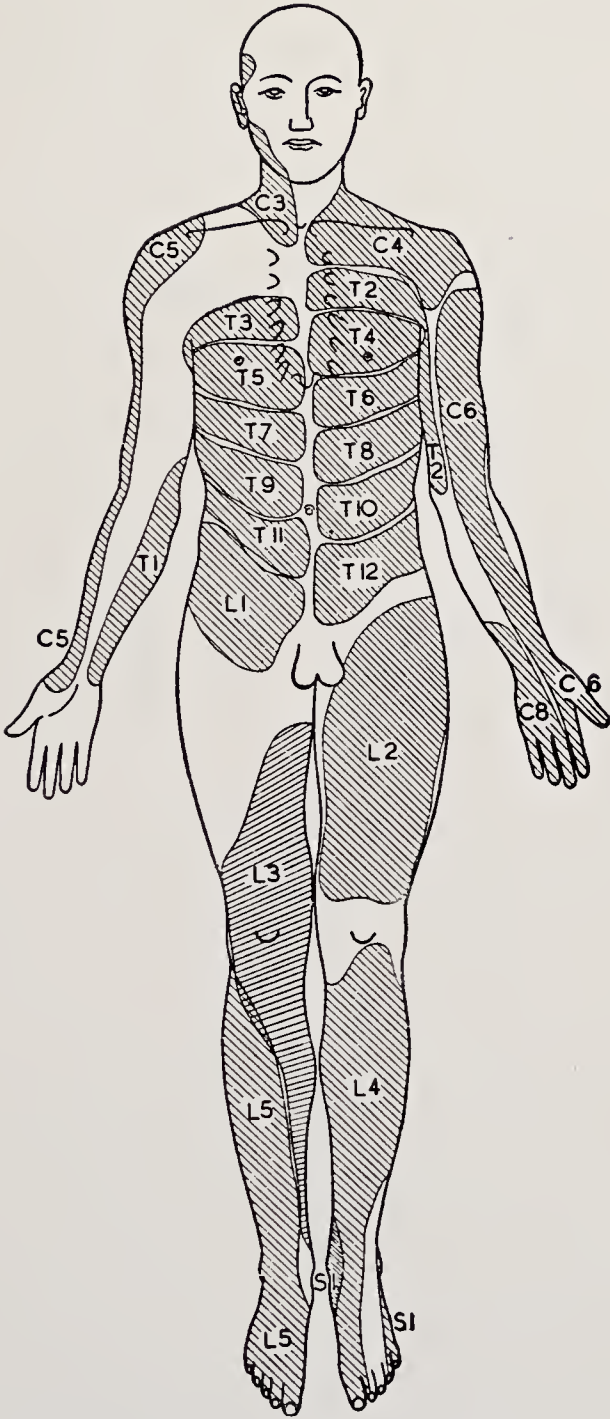


FIG. 12B. Dermatomes according to Foerster(1936)as redrawn by Lewis(1942a). Determined by the method of "remaining sensibility" on human cases.

sue spaces, renders the pain endings hyperexcitable. It is argued that the substance (or substances) appear at varying intervals, depending upon the character of the injury, the interval being short after a cut or a burn and longer after ischaemia or exposure to ultraviolet light. To quote:

"Pain nerve endings in this unusually responsive state react to warmth as do normal nerves to higher temperature; they react unusually to pinpricks and to light friction and to increased tension placed upon the skin directly or through vascular distension. The pain awakened from the tender skin in any of the several ways described is of one kind, and it is felt at the time of the interference, or almost so, and quickly subsides. There is in this time relation a strong suggestion that the immediate stimulus is direct and physical or that, if any intermediate process is set up, this must be a highly unstable or quickly reversible process.

"But this is not the only mechanism that brings pain from this hyperalgesia. The immediate pain response of rubbing or stretching subsides; but, after a little time, a second pain appears and lasts. The immediate pain must differ fundamentally from that of the recurrent pain. That the mechanism of the two differs is proved by the observation that previous arrest of the circulation to the skin in no way modifies the first, while it prolongs the duration of the second.

"When the susceptible skin is rubbed, the accompanying pain may be ascribed to direct stimulation of hyperexcitable pain nerve endings; the recurrent pain I attribute to a stable determinant of pain, the intercellular content of which is increased by rubbing. The prolongation of this recurrent pain by circulatory arrest follows naturally upon the maintenance of this raised content while the bloodflow remains obstructed.

"When pain is produced in injured skin simply by arresting the bloodflow to it and when the pain quickly subsides on releasing the circulation, I suppose that the substance has been passing out slowly into the tissue spaces, that it reaches an adequate concentration during circulatory arrest, and that the concentration rapidly declines to its former level at the release. As the concentration rises and falls, so does the excitability of the pain nerve endings, high concentration bringing stimulation and pain (Lewis, 1942a, pp. 66-67).

On exposure of the skin to 5° F. for two hours protein-containing fluid escapes into the tissue spaces amounting in three hours to 15% of the original volume of the part (Lewis, 1942b). The tissue injury thus induced by cold is associated with changes in the structure of the pain endings in the skin. Painful when first exposed the tissues later become numb, and after recovery from exposure they generally exhibit pain and hyperesthesia for 24 hours or more. Phenomena similar to these are exhibited by sailors adrift in open boats or pneumatic rafts. The loss of fluid into the tissue spaces may in these circumstances become extreme ("immersion foot") (see also White, 1943).

Attention must also be directed to the important monograph entitled *Pain mechanisms* by Livingston (1943) published as this book is passing

through press, too late for summary of its conclusions concerning the physiology of causalgia and related states.

SUMMARY

Magendie first demonstrated by means of section of the spinal nerve roots that the dorsal roots were sensory in function; through their fibres the segmental levels of the nervous system receive sensory impulses from the exterior and also from the interior of the body. Thirty pairs of such roots pass into the spinal cord, each being composed of myelinated and unmyelinated fibres; before reaching the cord the root breaks into a series of filaments and each individual filament has two parts: (i) medial made up of myelinated fibres, and (ii) lateral composed principally of unmyelinated and a few small myelinated fibres. On entering the spinal cord every fibre separates into an ascending and a descending division. Many of the larger medullated fibres go directly into the dorsal columns and pass thence to the gracilis and cuneate nuclei in the medulla. The six primary regions of termination of the posterior root fibres are: (i) ventral horn cells, (ii) intermediate grey matter, (iii) Clarke-Stilling columns, (iv) the dorsal horn cells, (v) substantia gelatinosa and (vi) gracilis and cuneate nuclei.

The more highly developed modalities of sensation are conducted to the spinal cord by fibres of large diameter. When examined by the cathode ray oscillograph, the fibres fall into three groups: A, B and C. Touch, pressure and the proprioceptive sense fall into the A group of larger fibres; they are the most susceptible to mechanical pressure and to oxygen lack. The B group are made up chiefly of small medullated fibres which convey thermal sensibility and localizable pain. The C waves come principally from unmyelinated fibres, some conveying less well localized pain, others, probably efferent vasomotor impulses. Pain, therefore, is distributed through the B and C group, localizable pain being probably conveyed by small medullated fibres, diffuse pain by the unmyelinated fibres. The more highly organized visceral afferent fibres have their cell stations in the dorsal roots.

Though not fully established certain evidence indicates that dorsal roots contain, in addition to the various categories of afferent fibre just mentioned, efferent vasomotor fibres responsible for the vasodilator effects of Stricker, Bayliss, Foerster and others.

The skin area, supplied by a pair of dorsal roots from a single seg-

ment, is referred to as a "dermatome." The extent of each individual dermatome has been determined in monkey and man by the method of remaining sensibility, *i.e.*, three roots above and three roots below the dermatome to be studied must be severed, and the margin of remaining sensory perception determined. By this means Foerster has established the extent of all dermatomes of man. Dermatomes outlined in this manner are larger but coincide in general position with the dermatomes defined by antidromic stimulation (vasodilatation and pilomotor reactions).

Aberrations of skin sensibility caused by mechanical, thermal, radiant or chemical insults are due to the liberation in the skin of a diffusable substance that reduces the threshold for stimulation of the pair endings (Thomas Lewis). Causalgia no doubt has a kindred origin.

III

THE MOTOR UNIT

HISTORICAL NOTE

With the recognition of the neuron as the ultimate unit of reflex activity, (His, 1889; Waldeyer, 1891) it became obvious that attention must be focused upon its individual activities, and that the function of the nervous system as a whole can only be explained in terms of the combined activity of its primary cellular units. For many years the individual neuron eluded isolation as a functioning entity, which made it impossible to analyze the brain and cord in simplest terms. Responses of single muscle fibres had been studied by Lucas (1909), Pratt (1917a&b) and others, but these studies had given almost no information concerning the characteristics of the nerve cell itself. As indicated in chapter II, the individual sensory neuron was the earliest to be isolated. Reactions of a single *motor* neuron, activated within the nervous system by a normal reflex stimulus, were first recorded by Derek Denny-Brown (1929a) while studying the stretch reflex of the isolated soleus muscle (decerebrate cat); since 1929 notable progress has been made in the analysis of their behaviour.

The motor unit was defined anatomically in the last century as the ventral horn cell and the group of muscle fibres which it innervates. No smaller unit of activity can be conceived, for when an impulse is started in the axon of a ventral horn cell, all peripheral structures innervated by the unit necessarily receive the impulse. But the ratio of ventral horn cells to muscle fibres in a given muscle had not been accurately determined until 1930; Tergast (1873) made nerve and muscle counts, but he failed to realize that nearly half the fibres passing to a muscle are sensory. He made the important observation, however, that the eye muscles (sheep) have a ratio of nerve to muscle fibres of about 1 to 3, whereas the corresponding ratio in limb muscles is of the order of from 1:80 to above 1:120.

ANATOMICAL CONSIDERATIONS

THE NEURON. The motor neuron has certain morphological characteristics that deserve close attention. It is made up of: (i) dendrites, (ii) cell body or soma and (iii) axon. The dendrites of the ventral horn cells ramify widely throughout the grey matter of the spinal cord, and it is estimated that dendrites and cell body of one motor neuron may be in contact with fibres from as many as 1,000 axon terminations of other cells in the nervous system (fig. 7; see also ch. IV). Thus on morphological grounds the ventral horn cells form a huge focus of convergence of fibres originating in other parts of the nervous system — a funnel col-

lecting the nervous impulses from a myriad of cells. Sherrington (1904) designated these motor units "the final common pathway of the nervous system" (ch. VIII). Fixed neurons contain conspicuous neurofibrils, but living dendrites examined under high power and dark field illumination are said to exhibit the simple structure of colloidal protoplasm without obvious morphological organization; but from time to time it has been urged that all nerve cells (and axons) contain neurofibrils and that these are the basis of conduction (Parker, 1929); moreover, recent studies (Weiss and Wang, 1936; Levi and Meyer, 1937) make it likely that neurofibrils, once thought to be artefact, are in fact structural entities of the living cell. That they have anything directly to do with conduction seems highly improbable, since all modern evidence indicates that the propagated disturbance in excitable tissues proceeds along the cell surface. The neurofibrils undoubtedly form the structural matrix of these elongated cells, and it is significant that they do not become conspicuous in tissue culture until the neuron begins to elongate (fig. 13c).

The cell body, or *perikaryon*, contains the nucleus and a well defined nucleolus; *mitochondria* are present in the cytoplasm, together with darkly staining "chromidial substance" generally referred to as *Nissl's granules* (fig. 13). The distribution and general appearance of these granules is affected by fixation (see Sheinin, 1932, and Bensley and Gersh, 1933a&b); with one fixation, however, their number and distribution varies with the physiological activities of the nerve cell. Normally they are absent from the region of the axon hillock, where the axon originates, but they are present in the proximal portions of all dendrites. In conditions of generalized fatigue, as in animals that have been kept awake for periods of 48 to 72 hours (fig. 13B), the Nissl granules tend to disappear, first from the base of the dendrites, later from the substance of the perikaryon. The Nissl substance also assumes importance in cells whose axons have been severed. In these circumstances, they suffer disintegration or "chromatolysis." When the axon is severed close to the cell body, marked dissipation of Nissl substance occurs, sometimes described as "tigrolytic" reaction because of the tigroid appearance of the cytoplasm. The change is also referred to as "retrograde degeneration" and is extensively used for localization of nuclei and fibre systems within the brain and spinal cord (ch. XVII). Occasionally also, cells within the nervous system which are suddenly deprived of their connection with other parts of the nervous system exhibit chromatolysis. This is designated "transneuronal degeneration." Transneuronal degeneration is rare, but occurs in the lateral geniculate body when lesions are made in the retina, and also in several other highly organized nuclei which depend upon a single source of afferent influence.

Another structure found in the cell body is the so-called *Golgi apparatus* (fig. 13A), a complex reticulum restricted to the cytoplasm, but generally found near the nucleus. The changes which it undergoes when an axon is cut are principally a movement of the substance toward the periphery of the cell "retispersion," fol-

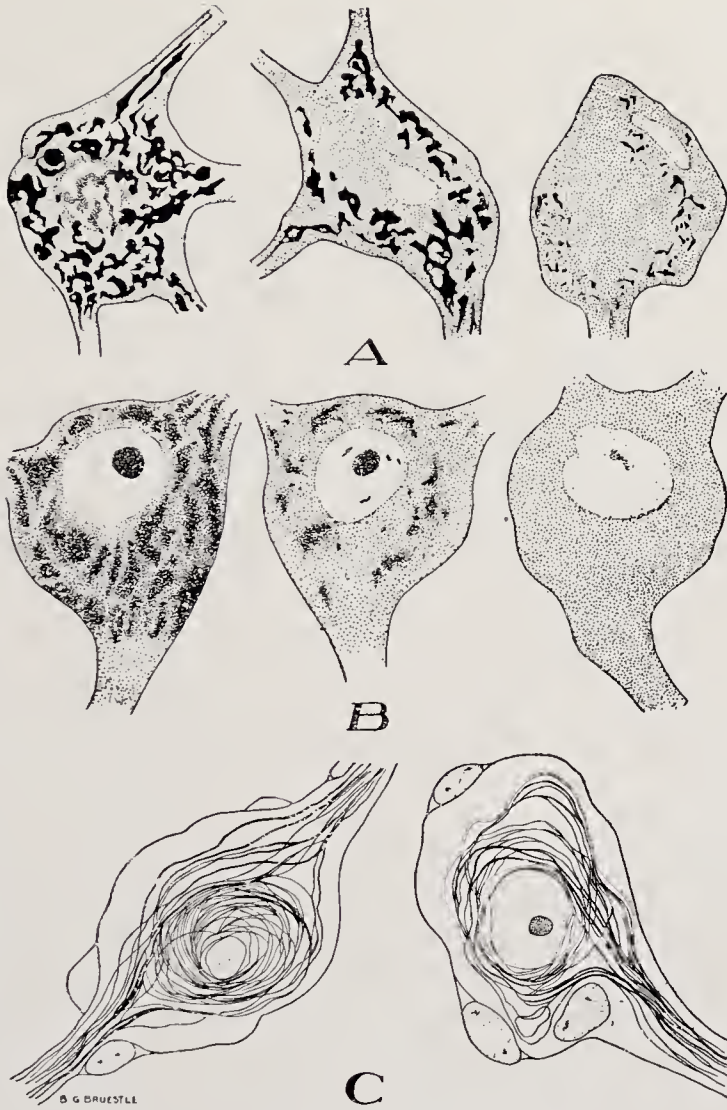


FIG. 13. Principal structures of spinal cord neuron, and changes which these structures undergo as a result of injury. A, Golgi apparatus: left, normal cell; middle, retispersion 7 days after section of axon; right, retisolution after section of spinal cord(after Penfield, 1920). B, Nissl substance: left, normal cell; middle, moderate chromatolysis, from fatigue; right, extreme retrograde chromatolytic degeneration(after Dolley, 1913). C, Neurofibrils in living ganglion cells of 8-day chick embryos cultivated 7 days in tissue culture(tracing from photograph, Weiss and Wang, 1936).

lowed by subsequent fragmentation, or "retisolution." According to Penfield, (1920) the Golgi apparatus is an even more sensitive index of activity of the nerve cell than the state of the Nissl substance(Cowdry, 1932). The present status of the Golgi apparatus in nerve cells has just been fully discussed by Kirkman and Severinghaus(1938). In the living state there is specialization of structure in

the axon hillock and some have suggested that the nerve impulse originates in this region.

The minute structure of the axon itself cannot concern us in this book; suffice to say that when an axon is severed from its cell body the axon degenerates distally to the section, and the proximal trunk tends to regenerate if it is provided with Schwann cells (see Young, 1942). Regeneration of cut axons does not occur in the brain or spinal cord in higher forms, although Sugar and Gerard (1940) have recently adduced convincing evidence of spinal cord regeneration in the rat. The first morphological change to occur when an axon is severed from its cell body is in the motor end plate (swelling and chromatolytic changes like those found in the perikaryon), as was first established by Ranvier (1874). A similar phenomenon occurs in the central nervous system, namely, that the first change following section of an axon is in its terminal bouton. Degeneration then proceeds, sometimes from the distal towards the proximal end of the fibre, but more often throughout the entire length of the fibre simultaneously (Sugar, 1938); these changes, first described in 1850 by Waller, have since been known as "Wallerian degeneration." For further details concerning degeneration within the central nervous systems, see Ramón y Cajal (1928).

Regeneration of peripheral nerve. Factors influencing the rate of regeneration of cut peripheral nerve were studied intensively during the first World War and the problem has been taken up anew since 1939. It has been ascertained by J. Z. Young (1942), Weddell and others in both man and animals that a healthy motor nerve regenerates at the rate of approximately 4 mm. each 24 hours. If a nerve is re-united after being severed some 8 days elapse before the nerve bridges the gap to grow outward into the degenerated trunk. After that initial delay if satisfactory union has been established the 4 mm./day regeneration continues until the nerve reaches a sensory end organ, or a muscle fibre, after which another 7 or 8 day interval passes before a *functional* union is established. Hence if a nerve is severed at 8 cm. from its muscle a minimum of 5 to 6 weeks must elapse before signs of functional activity can be expected.

Young finds (1942, p. 346) "that after severance and primary suture, whether by stitches or by the plasma method, fibres grow at 3.45–0.16 mm./day in the rabbit. There is a latent period of 7.3 days before any fibres appear in the peripheral stump, and this figure also lies within the limits estimated by Cajal and others using histological methods.

"In cases in which the nerve was not divided but the axons were interrupted by thorough crushing with fine forceps, the rate of growth was found to be higher, namely, 4.36–0.24 mm./day. This type of injury interrupts all the axons, which undergo Wallerian degeneration, but the connective tissues maintain continuity, and provide optimal conditions for outgrowth. The latent period is shorter, 5.2 days, than after suture, which is not surprising, but it is interesting to find

that the axons advance faster along the peripheral stump than they do after suture.

"Further experiments have established that in the rabbit there is no great difference between the rate of advance of the axon tips in the different divisions of the sciatic nerve. Nor is there any difference in the rate after lesions made high up in the thigh or below the knee. However in the rabbit the differences in distance from the cord involved in such experiments cannot be made great, and it is possible that in man this problem of the rate of outgrowth at different levels is more complex."

The mode of reuniting a severed nerve affects rate of regeneration, and also the delay at the junction. Young and his colleagues introduced the successful technique of "plasma suture"—concentrated plasma being applied as "glue" to hold the two ends of the nerve in firm approximation, rather than using gross surgical sutures to reunite a myriad of delicate "silken" nerve strands. Nilson de Rezende(1942) has used 20% gum acacia for the same purpose and Paul Weiss(1943) employs arterial wall, pulling the two ends of the severed nerve into an arterial lumen of diameter similar to the nerve. Both methods favor rapid union without the gross mechanical distortions caused by suture. Longer gaps resulting from violent injuries, *e.g.*, from bomb fragments, are bridged by the use of nerve grafts—usually of fixed or frozen nerve(Weiss, 1943), the lipids of the dead nerve serving to direct the course of the regenerating fibres(see also Sanders, 1942).

PHYSIOLOGICAL ANATOMY. Modern study of the motor unit began in 1925 when Sherrington first used the term, and later defined it as "an additive assembly of 'motor units,' meaning by motor unit an individual motor nerve fibre together with the bunch of muscle fibres it innervates" (Eccles and Sherrington, 1931). In the cat's tenuissimus muscle as many as 140 to 160 muscle fibres were innervated by a single motor nerve fibre(Porter and Hart, 1923). Such a ratio demands the existence of extensive peripheral branching of individual nerve fibres, a point clearly established histologically by Cooper(1929) and subsequently studied by Denny-Brown, whose excellent figure is reproduced in chapter 1(fig. 3).

Average unit tensions. The subject was further elucidated in the now classic paper of Eccles and Sherrington(1931). Using cats from which appropriate dorsal root ganglia had been removed, and the sensory fibres to particular muscles degenerated, they determined the average tension value of each nerve fibre passing to a group of representative muscles. They thus were able to answer the basic question of how much tension a single motor unit is capable of controlling in a given muscle. In their deganglionated preparations, they measured by direct motor nerve stimulation the total tension developed in a twitch and in a tetanus(*m. soleus*, *extensor longus digitorum* and *gastrocnemius*); later the motor nerve fibres supplying the muscles in question were enumerated, and the value

so obtained was divided into the total tension development previously observed. The figures arrived at for the tetanus were surprising and are as follows:

	<i>Gm.</i>	<i>No. units</i>
Gastrocnemius (medial head)	30.1	430
Soleus	9.9	200
Semitendinosus	5.5	630
Extensor longus digitorum	8.6	330
Crureus	10.2	250

For the twitches of these muscles the tension values were approximately a third to a quarter of the amount recorded for the tetanus. From these calculations the surprising fact is revealed that a single anterior horn cell of the gastrocnemius muscle of the cat is capable of developing not less than 30 gm. of tension. Since these are average figures, it is clear that some develop more tension than this and some less.

Innervation ratios. The anatomical basis of these large units of tension lies in the branching of nerve fibres (Cooper, 1929). Eccles and Sherrington studied the number of nerve fibres in a cross section at various distances from the spinal cord; as indicated in their diagram (fig. 14), they observed a considerable increase in number in the more peripheral cross sections. The deafferented nerve to gastrocnemius medialis was found to have 662 motor fibres at its beginning and 815 at the most distal point examined. Actually the principal dichotomy occurs well in the fleshy parts of the muscle and hence cannot be determined by this method (see fig. 3). Eccles and Sherrington observed furthermore that when the diameters of the motor fibres were counted they fell into two groups: (i) a large number of approximately 4 *microns* and (ii) a group ranging from 14 to 15 *microns*. Both groups pass directly from the ventral nerve root and are unaffected by removal of the sympathetic ganglia. Since the posterior root ganglia had been removed in these preparations, the remaining fibres were clearly somatic motor fibres. Eccles and Sherrington infer that small fibres probably innervate small units, and that the large fibres innervate the larger motor units. The nervous system thus retains the capacity to throw in large units, and presumably delicacy of adjustment is made possible through interaction of the two. The large fibres, however, form only 66.3 per cent in point of numbers, but they occupy 92.4 per cent of the total cross sectional area. Therefore the principal units in the muscles examined were large units.

Tergast (1873) found, without allowing for sensory fibres, a low inner-

vation ratio for eye muscles and a high ratio for muscles to the extremities. Tenuissimus, a flexor of the cat's hip, has a ratio of 1 nerve fibre to approximately 150 muscle fibres(Adrian, 1925). Complete enumeration

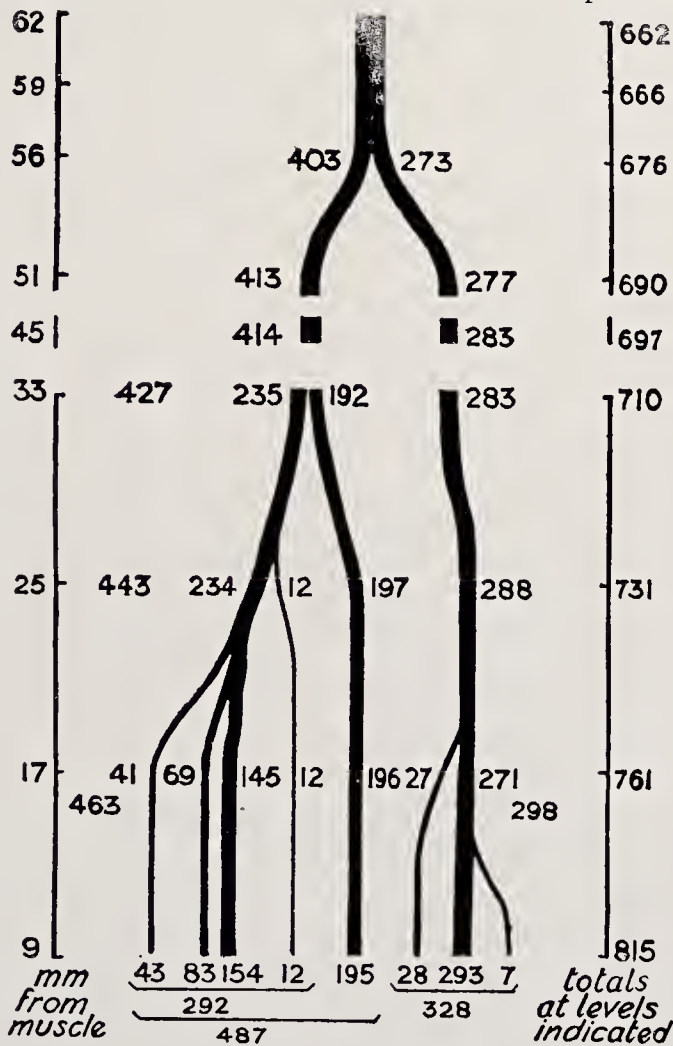


FIG. 14. Eccles and Sherrington's diagram(1930)showing their fibre counts of nerve to m. gastrocnemius medialis during 53 mm. of its course towards the muscle. Motor fibres thus undergo bifurcation before nerve reaches muscle(*Proc. roy. Soc.*, 1930, 106B, p. 331).

of all muscle and nerve fibres in the cat's soleus(red muscle)and extensor longus digitorum(white)was undertaken in 1931 by Clark. Posterior root ganglia supplying these muscles were removed some weeks prior to examination. He then counted the motor nerve fibres supplying each muscle and enumerated the muscle fibres themselves. He also deter-

mined the average tension developed by each unit. For soleus an innervation ratio of 1 to 120 was established and for extensor longus digitorum 1 to 155. This means that when one anterior horn cell to soleus is stimulated an average of 120 muscle fibres is thrown into action. For extensor longus digitorum the ratio was 1 to 165. Clark's results are tabulated as follows:

<i>Muscle</i>	<i>Wt. per muscle fibre</i>	<i>Tension per muscle fibre</i>	<i>Tension per nerve fibre</i>	<i>Innervation ratio</i>
	<i>mgm.</i>	<i>mgm.</i>	<i>grams</i>	
M. soleus	0.122	84.0	8.6	1:120
M. extensor long. digit.	0.072	48.5	9.9	1:165

Unfortunately no innervation ratios have yet been determined for muscles of primates. There is reason to believe, however, in view of Tergast's enumeration, that muscles which execute finely adjusted movements such as the extraocular muscles or the muscles of the ear, have far smaller innervation ratios than those which ordinarily take part in gross patterns of response such as the flexor reflex. Similarly it may be anticipated that the fibres to the primate digits have a smaller innervation ratio than the more proximal muscles of the extremity; indeed, it is likely that muscles which have an extensive representation in the motor area of the cortex have smaller innervation ratios than those which do not(ch. xx).

FUNCTIONAL ACTIVITY OF SINGLE UNITS

Direct evidence concerning the tension development of single units, as well as their rate of discharge, has been obtained by Denny-Brown (1929a), Eccles and Sherrington(1930)and Clark(1931).

RATE OF DISCHARGE. While studying the stretch reflexes of the soleus muscle, Denny-Brown observed that mild degrees of stretch applied to the tendon cause a regular sequence of small galvanometer deflections which can be recorded with the unaided string galvanometer(fig. 15). Although the enumerations of Eccles and Sherrington were not then available, Denny-Brown(1929)rightly inferred that these regular deflections represented the group of fibres innervated by a single anterior horn cell. If the stretch stimulus were then slightly increased, a second group of action currents appeared, generally discharging at a different rhythm from the first, and therefore waxing and waning with the primary series. These secondary action currents arise from activity of an addi-

tional anterior horn cell. With higher degrees of stretch, more and more units come in, and the electrical deflections in these circumstances become confused and indefinite (Fulton and Liddell, 1925). Using another technique, Adrian and Bronk (1929) succeeded, quite independently of Denny-Brown, in obtaining action currents from single units in other muscles. Instead of employing the stretch reflex, they utilized the method of "cutting down" the motor nerve to a muscle so that only two or three fibres remained in functional continuity with the



FIG. 15. Action currents of single units of cat's soleus muscle responding to slight stretch; recorded by unaided string galvanometer. In upper record a unit *a* waxes and wanes with *b*, but drops out towards end of record leaving *b* alone. In lower record waxing and waning of two units discharging at slightly different rates is seen (Denny-Brown, *Proc. roy. Soc.*, 1929, 104B, pl. 11, figs. 4A and 4B).

nervous system. Action potentials were then recorded from a nerve trunk distal to the dissection and various reactions such as the flexor reflex were evoked by pinching the foot. In this way the rate of discharge of various units responding to several types of reflex stimulation was recorded.

In Denny-Brown's studies, the spontaneous action current rhythm of the red-fibred soleus never exceeded about 10 per sec., and the average rate of discharge for these red muscle units was of the order of 5 to 7 per sec. In Eccles and Sherrington's reflex tetani of soleus, the highest rate observed was 13.7. Turning to *white* muscle fibres, Adrian and Bronk also recorded remarkably low rates of discharge even under intense stimulation (fig. 16). For pain stimulus applied to the foot, the discharge began at 5 to 6 per sec., and ultimately attained a rate of 20 per sec. Within an extensor nerve, the most rapid rates were 20 to 25 per sec. at the outset, ultimately reaching, at the height of crossed extensor

response, 80 to 90 per sec., and never more than 100. Adrian and Bronk's observations indicate that the stronger the stimulus the more rapid the rate of discharge, and rate, therefore, becomes an important variable in determining the gradation of contractions of skeletal muscles. They noticed that alterations in rate were more readily demonstrated in extensor muscles than in the more primitive flexor reactions.

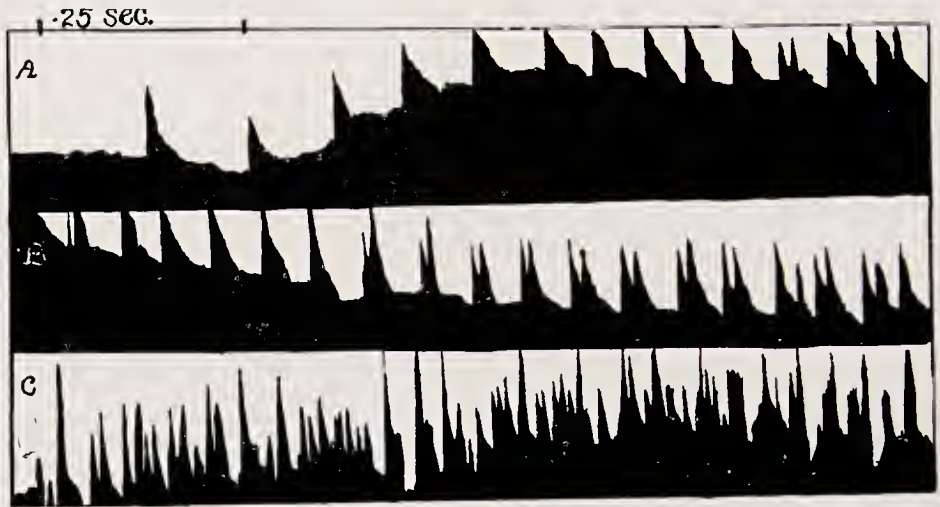


FIG. 16. Capillary electrometer record of volitional contraction of human triceps obtained with concentric needle electrodes. In A, one unit only is responding, at first slowly and then more rapidly; a second unit appears in B which waxes and wanes with the first. In C, a large number of units are responding (Adrian and Bronk, *J. Physiol.*, 1929, 67, p. 134).

Single units were also placed under direct observation during volitional contraction by the use of small concentric needle electrodes directly inserted into the investigator's biceps muscle. As indicated in fig. 16, contractions generally begin slowly at 5 to 6 per sec., then as the magnitude of the contraction becomes greater ultimately reach rates of 30 to 40 per sec. and rarely as high as 50. Examining tonic muscles which maintain postures in reaction to gravity, Adrian and Bronk, in harmony with Denny-Brown, also found remarkably low rates of discharge varying from 5 to 10 per sec. in cat as well as in man.

It is thus apparent that if more than two fibres are brought into action, each one discharging out of phase with the next, the electrical result will be a complex series of deflections, which give little information about the individual unit itself. Such records are readily obtained on gradually increasing any type of reflex response in the large muscles:

first one unit, then another, later three or four come in and ultimately a number so large that the electrical record is quite meaningless ("recruitment"). Analysis of these reactions indicates two facts of vital importance to the physiology of the nervous system: (i) that gradation of motor activity may be achieved, especially in extensor muscles, by variation of the rate of discharge of individual units (cf. ch. I on rates of end organs), (ii) long sustained responses such as those underlying postural mecha-

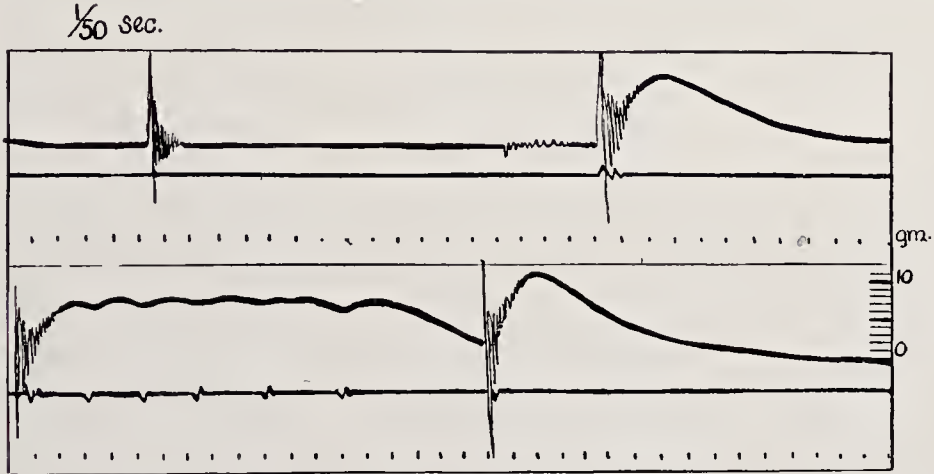


FIG. 17. Simultaneous electrical and mechanical records of motor units of cat's soleus in response to tendon tap. In lower record a repetitive response is seen in response to similar tap followed by single jerk response. In each case tension developed was less than 10 gms. Repetitive response in lower record indicates that only a single unit is responding (Eccles and Sherrington, *Proc. roy. Soc.*, 1930, 106B).

nism (ch. VII) are maintained by rates of discharge ranging from 5 to 15 per sec., and at this rate a fibre can discharge indefinitely without apparent signs of fatigue.

TENSION DEVELOPMENT. Tension has been measured in a number of instances when a single unit is responding. Thus Denny-Brown (1929) made a rough estimate that when a single soleus unit discharged the tension development lay between 1 gm. and 20 gm., but his levers did not permit accurate determination. Eccles and Sherrington (1930) succeeded in obtaining individual tendon jerk responses of single units (fig. 17) and the response was never less than 1.5 gm. and in a given series they increased by the following increment: 0, 0, 2.5, 2.5, 4, 6.5, 6.5, 6.5, 6.5, 7, 8.7, 10.5. From this they concluded "there seems no reason to doubt that the 2.5 gm. responses are twitches of single motor units, and the 4

gm. responses of 2 units. Continuing the series it seems likely that 6.5-7 gm. is given by 3 units, 8.5 gm. by 4 units and 10.5 gm. by 5 units. In this series 2.5 gm. is the greatest tension of a single unit and 1.5 gm. is the smallest. Further observations during the experiment accorded perfectly with these values; in all cases 1.5 or 2.5 gm. was the tension produced by a single unit." Since these active units are "smothered" in a large muscle mass of inactive fibres, it is improbable that this full tension value is registered at the tendon. It must be recalled also that units vary in size; whether the larger or the smaller units have the higher threshold in the reflexes under discussion has not been determined.

POLIOMYELITIS AND THE MOTOR UNIT

The concept of the motor unit is of great importance to an understanding of the pathological physiology of poliomyelitis and certain other degenerative diseases of the central nervous system such as amyotrophic lateral sclerosis. When a ventral horn cell succumbs to poliomyelitis virus all the hundred odd muscle fibres which it innervates become atrophic and ultimately die. This cluster of muscle fibres generally forms a closely knit group within the muscle itself and the Swedish pathologist, Gunnar Wohlfart, has observed in poliomyelitis(1937) and amyotrophic lateral sclerosis(1941) that muscle degenerations follow the pattern, not of muscle fibres, but rather of discrete muscle fasciculi. In examining sections of atrophic poliomyelitis muscles, one frequently finds complete atrophy of all striated fibres in a given fasciculus, while in the next fasciculus the majority of fibres appear to be healthy and intact. It is possible, therefore, that the muscle fasciculus may represent the motor unit. Occasionally, however, only half or a third of a fasciculus is affected, but in those instances the degenerating fibres are closely grouped and are not scattered indiscriminately throughout the fasciculus.

Denny-Brown and Pennybacker(1938) point out that in certain irritative neuromuscular diseases, individual muscle fibres are affected in such a way as to give rise to fine twitching along the muscle surface. This is true "fibrillation," resulting from abnormal irritability of individual muscle fibres. "Fasciculation," on the other hand, involves large groups of fibres which tend to respond simultaneously and involuntarily. Fibrillation arises from disordered metabolism of the individual muscle fibre, whereas fasciculation stems from irritative disorders of

the ventral horn cell or its axon. Fasciculation may occur in the early non-paralytic stages of poliomyelitis.

In considering the physiological anatomy of poliomyelitis and therapeutic measures designed to benefit such patients, one must therefore recall that it is the motor unit which degenerates. At one time it was believed that complete immobilization of affected extremities was essential; but since this leads to atrophy of healthy units, as well as those with degenerated nerve fibres, rather should one encourage massage and freedom of movement in order to maintain the healthy motor units of paretic muscles in a state of maximum physiological capacity.

SUMMARY

The motor unit is the basic motor element of the reflex arc; it consists of an anterior horn cell of the spinal cord and the group of muscle fibres which it innervates. The anterior horn cell consists of dendrites, cell body(perikaryon)axon and end plate(which contains muscle fibre nuclei). The dendrites ramify profusely in the grey matter of the spinal cord, receiving impulses from many posterior roots and from all levels of brain and cord. The dendrites and cell body are covered with synaptic terminals from other neurons. The cell body contains nucleus and nucleolus, together with various organized elements in its cytoplasm, such as neurofibrils, Nissl substance, Golgi apparatus and carotinoid pigments. All of these substances exist in the living cell, but knowledge of their organization is based principally on fixed preparations. The axon presumably begins at the axon hillock and extends thence via the ventral nerve root to peripheral nerve and muscle. The functional activities of the axons correspond closely, except in time relations, with the nerve cell body and its dendrites.

The motor unit has been studied in animals from which appropriate posterior root ganglia have been removed and time allowed for sensory fibres to degenerate. In such preparations stimulation of representative muscle nerves causes measurable tension values. After the tension has been determined, the nerve is sectioned, its fibres enumerated, and the total number is divided into the tension value of muscle as a whole. This has given the surprising result that in the gastrocnemius a single anterior horn cell is capable, through repetitive discharge, of developing an average of 30 gms. of tension. Other more distal muscles have smaller unit values.

The innervation ratio refers to the proportion of nerve to muscle fibres. In extensor longus digitorum the ratio is 1 to 165; in soleus 1 to 120. In muscles designed for more discrete movement, such as the extraocular muscles, the ratios are much smaller.

The activities of individual motor units have been placed under direct observation. Their tension values have been measured and vary from 2 to 8 or 10 gms., but since they operate within the incubus of a large muscle mass, the actual tension values are probably not realized. In ordinary reflexes the rate of unit discharge is surprisingly low: for red muscles 5 to 7 per sec.; for white muscles seldom more than 15 to 25 per sec. The individual motor unit, therefore, discharges normally at a relatively low rate.

In poliomyelitis degeneration occurs in terms of motor units, rather than of individual muscle fibres; in many instances motor units are represented by whole muscle fasciculi.

IV

SYNAPSES AND ELEMENTARY REFLEXES

HISTORICAL NOTE

According to Robert Whytt(1755), the so-called "fundamental experiment" of reflex physiology was first carried out by Stephen Hales, who about 1730 had noted that, although the legs of a decapitated frog would withdraw on being pinched, such "reactions" disappeared forever when the spinal cord had been destroyed("pitched"). Whytt repeated the experiment and elaborated upon it, incidentally introducing modern terminology by referring to a "stimulus" and a "response." Unzer(1771)first employed the word "reflex" to describe this type of sensori-motor reaction. The reflex concept was further crystallized by the discoveries of Magendie and Bell described in chapter II. Marshall Hall(1833)did much to advance the reflex concept by his analysis of segmental, intersegmental and suprasegmental reflexes. "The spinal cord," he said, "is a chain of segments whose functional units are separate reflex arcs, which interact with one another and with the higher centres of the nervous system to secure coordinated movement." Thereafter little advance was made in the analysis of segmental reflex mechanisms until the epoch-making work of Sherrington(1899)which was summarized in his Silliman Lectures, *The integrative action of the nervous system* (1906). For further historical details see Fearing's excellent monograph(1930).

THE simplest reaction of the nervous system is the segmental reflex, a reaction evoked by afferent impulses entering the spinal cord at the level from which the motor impulses emerge. Reflexes of this type can be evoked from the extremities of spinal animals, but actually the motor effect is seldom confined to a single spinal segment. This at once introduces one of the basic concepts in the physiology of the brain and spinal cord, namely, that *the central nervous system is organized, not in terms of anatomical segments, but in movement patterns*. Hughlings Jackson once said, "The simplest spinal reflex 'thinks,' so to say, in movements, not in muscles"(Sherrington, 1931, p. 21). Therefore, when the foot of a spinal animal is pinched, the resulting reflex is not restricted to muscles of the dermatome stimulated, but a withdrawal of the whole limb occurs. This is the familiar *flexion reflex* which involves the flexor muscles of hip and knee and ankle, as well as those of the toes. The significance of the flexor pattern of response will be discussed in chapter VI, and concomitant reactions in other extremities in later chapters.

GENERAL CHARACTERISTICS OF REFLEXES

Since the flexor reflex is one of the simplest of segmental reactions, it is useful for analysis of certain basic features of the central nervous system. These are: synapse, reflex latency, summation, refractory period, the excitability cycle and synaptic transmission.

THE SYNAPSE. Before discussing the reflex, the anatomical characteristics of the "synapse" will be described. Foster and Sherrington introduced the term synapse in 1897 to describe the normal anatomical relation between contiguous neurons.* The neuron doctrine, which is based on the work of van Gehuchten(1891), His(1889), Forel(1887) and Ramón y Cajal(1933), presupposes that each functional unit of the central nervous system is a cell which has no direct anatomical continuity with any other functionally related cell in the nervous matrix, action of one cell upon another being communicated solely through discontinuous interfaces. The name neuron was suggested by Waldeyer in his well-known statement of the neuron doctrine(1891). The papers of Ramón y Cajal demonstrating the free endings of axons within the nervous system and the cone of growth of the neuroblast were published in 1888-1890.

The latest and most authoritative statement of the histological basis of the neuron doctrine is that of Ramón y Cajal(1933)—his final paper dealing with the subject to which he had devoted his entire scientific life. The neuron doctrine, originally contested by Golgi whose staining methods had made possible its enunciation, is still doubted in certain quarters; however the large body of evidence marshalled by Cajal and others showed that degeneration goes up to, but does not involve, the contiguous cell. The endings of degenerating axons in the spinal cord swell up and completely disappear within five to six days, leaving no sign of injury or change in the cells on which they terminated. Tiegs(1927, 1931), Boeke(1932) and Stöhr(1935) have been able to stain minute threads of tissue passing from terminal nerve fibre to nerve cell, but the non-nervous nature of these strands has been emphatically demonstrated by Nonidez(1936). Lawrentjew(1934) has recently shown their existence to depend on the concentration of formalin used in tissue fixation, and Stöhr's "periterminalreticulum" is pres-

* In a recent personal communication Sherrington writes: "You enquire about the introduction of the term 'synapse'; it happened thus. M. Foster had asked me to get on with the Nervous System part(Part iii) of a new edition of his 'Text of Physiol.' for him. I had begun it, and had not got far with it before I felt the need of some name to call the junction between nerve-cell and nerve-cell(because the place of junction now entered physiology as carrying functional importance). I wrote him of my difficulty, and my wish to introduce a specific name. I suggested using 'syndesm'(*σύνδεσμος*). He consulted his Trinity friend Verrall, the Euripidean scholar, about it, and Verrall suggested 'synapse' (from *συνάπτω-αψω*[clasp]) and as that yields a better adjectival form, it was adopted for the book."

ent after complete denervation of structures (Kolossow and Polykarpowa, 1935). The so-called transneuronal degeneration which occurs in the visual system (ch. xvii) and spinal cord is regarded as due to isolation "dystrophy." Barnard's recent claim (1940) that ventral horn cells lose the synaptic endings that surround them following section of the ventral root was promptly contested both by Barr (1940) for spinal nerves and Schadewald (1941) for trochlear and abducens nuclei. Miss Barnard's deductions are wholly contrary to the neuron doctrine, and so far they have been entirely unconfirmed (Schadewald, 1942).

In all parts of the central nervous system including the sympathetic ganglion chain (Gibson, 1940) the axon ending forming the proximal interface of the synapse has a characteristic morphological structure which in the majority of cases takes the form of an irregular bulbous enlargement or varicosity, called by its discoverers (Held, 1897) "Endfüsse" (end feet) and "Endkolben" (terminal knobs).^{*} Fibres from the dorsal root entering the spinal cord bifurcate (ch. ii) and give off collateral branches which, after fibrillar division, terminate in many bulbous expansions on the cell body or upon the dendrites of another neuron (fig. 18); thus each fibre has synaptic connection with a large number of neurons. The sensory fibres concerned in the segmental reactions just mentioned may terminate immediately they enter the spinal cord, generally upon internuncial neurons (fig. 6, ch. ii). Since the majority of neurons originating within the nervous system terminate in this characteristic manner, the larger motor cells such as those of the ventral horn may be covered by more than a thousand of such synaptic endings from fibres of the dorsal root, from other segments of the spinal cord itself, and from suprasegmental levels (fig. 18). According to Barr (1939) at least 38 per cent of the ventral horn surface is covered by bouton endings.

The actual distribution of these terminal bulbs from any given source, e.g., a dorsal root fasciculus, can be determined by virtue of the fact that the endings, following section of the axons which give rise to them, swell and begin to disintegrate within 24 to 72 hours after severance of their parent fibres; after 120 hours spinal cord terminals granulate

^{*} The structure of the synapse is best known from Ramón y Cajal's paper (1903) in which he variously designated these axon terminations as "pies" (feet), "mozas" (knobs), "anillos" (rings), "varicosidades" (varicosities), "bulbos" (bulbs) and "botones" (buttons). The last term in its French form "boutons" has been widely adopted, even in the English literature; but it is not a happy term and Cajal himself seldom used it. Many adhere to considerations of priority and employ Held's original designation in its English equivalent of "end feet." Alternative phrases such as terminal knobs or bulbs, and boutons terminaux will no doubt be retained in the literature. The Golgi method of staining end feet gives a more faithful picture of these synaptic swellings than silver methods because it stains them all, large and small (Lorente de Nó, 1934), even on thin dendrites, whereas the silver impregnations bring out only the larger endings.

and disappear (fig. 19). In this way it has been established that the majority of fibres entering the spinal cord by the dorsal root terminate, not upon cells of the ventral horn, but upon internuncial neurons of the intermediate grey matter of the spinal cord (Hoff, 1932, Foerster, *et al.*, 1933). Some fibres cross to the other side of the spinal cord to terminate there on internuncial neurons, and a few — not more than



FIG. 18. Drawing of section through ventral horn cell in cervical region of cat's spinal cord. Cajal's reduced silver nitrate method. Mag. approx. $\times 750$. Note large number of end bulbs on surface of cell body and proximal portion of dendrites. Dorsal and ventral surfaces of the cell are in adjacent sections (from M. L. Barr, *J. Anat.*, 1939, 74, 5).

2 to 3 per cent in the lumbar segments of the cat — actually pass directly to the anterior horn cells. So it is possible to conceive of a reflex response involving only two elements; a sensory neuron and an effector motor horn cell. Actually, however, most reflexes involve at least one intercalated neuron (fig. 8).

There has recently been some discussion of the silver technique as a means of determining the site of termination of pathways within the nervous system. Thus H. A. Davenport, who in 1933 published an account of the staining methods used by Hoff, has recently (Phalen and Davenport, 1937) studied the normal distribution of end feet in the spinal cords of monkeys, dogs, cats, rats, rabbits and other vertebrates. He reports marked variations in their size and form, especially in monkey, cow and pig and believes that the variation in size is so great nor-

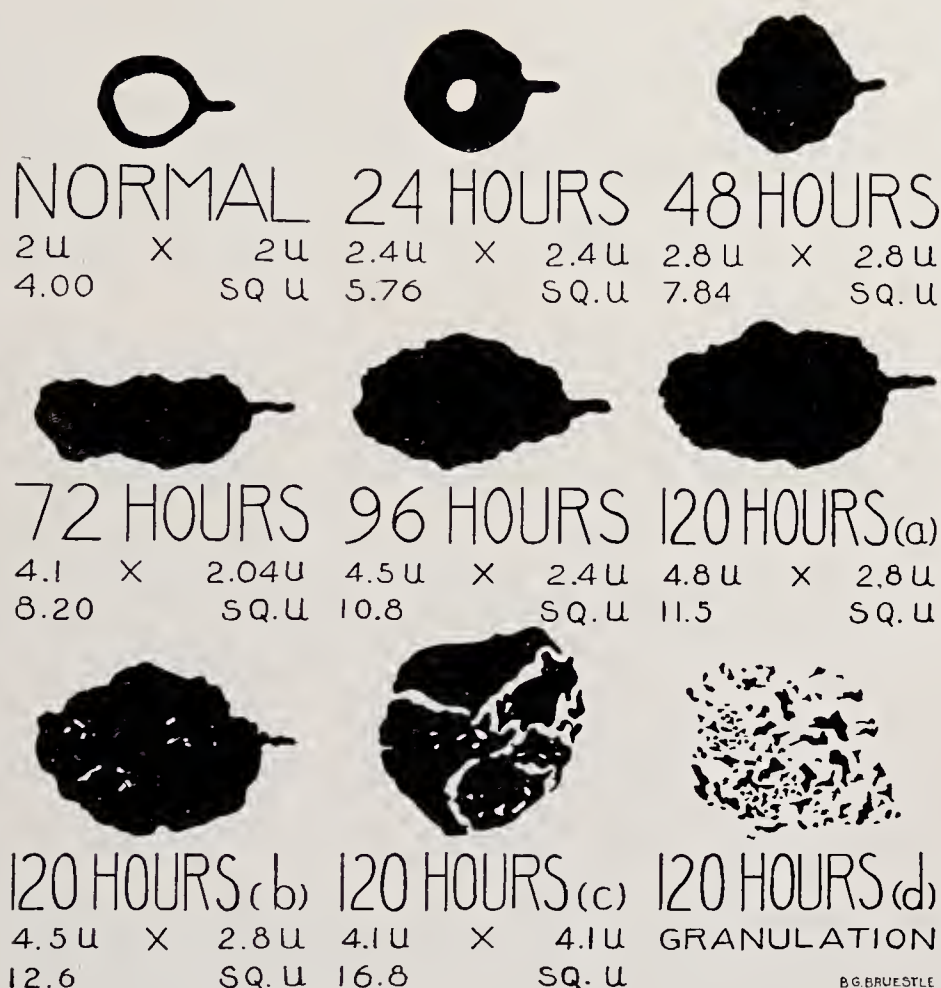


FIG. 19. Degenerating synaptic terminals; a diagram showing nine stages in degeneration of terminal bouton in spinal cord of cat at several intervals following section of dorsal nerve root. Normal ending is seen in upper left, and final stages of fragmentation and granulation are illustrated in various samples drawn from a 120-hour degeneration. By 150 hours boutons have disappeared entirely (W. C. Gibson, *Arch. Neurol. Psychiat.*, 1937, 38, 1147).

mally that it is often quite impossible to differentiate normal from degenerating endings. Similar conclusions have been reached by Bodian (1936, 1937), and by Minckler (1940, 1941). From the work of these investigators and the earlier studies of Hoff, it is clear that distinction between the normal and the degenerating endings is often difficult to make, and in specific instances it may be impossible; but improved methods of fixation will doubtless overcome many present difficulties. Ramón y Cajal (1903) originally insisted, and Lorente de Nó (1934a, 1938) and others have since confirmed it, that the range of size of well fixed synaptic endings of the cord is, in point of fact, small in higher vertebrates. The studies

of Gibson(1940)who succeeded in staining the preganglionic terminations in sympathetic ganglia as well as the larger end feet of the cerebral cortex, together with the similar work on sympathetic synapses of Lawrentjew(1934), are also in agreement in indicating that degenerating boutons are clearly recognizable in well fixed tissue; similar observations have been made by Snider(1936)in studying the degenerating "mossy" endings in the cerebellum, but the capricious character of the Golgi and the silver staining techniques makes essential the greatest possible caution in interpreting results. At present there is no reasonable doubt that the stages in the degeneration of synaptic endings in the spinal cord are essentially as depicted above in figure 19(see Federov, 1935a&b).

REFLEX LATENCY. Since the rate of conduction in sensory and motor nerve fibres is approximately known, the time occupied by nerve conduction in any given reflex response can be estimated with some accuracy. When these intervals are subtracted from the total latent period of a reflex, the remaining interval—called by Jolly(1911)the "central reflex time"—may be taken to represent the delay within the spinal cord, presumably the "synaptic delay." In the case of the flexor reflex of a spinal cat, the apparent latency of the reflex was 10.4 msec.(Eccles, 1936b).

	<i>msec.</i>
Conduction time in afferent nerve (31.6 M. per sec.)	4.4
Conduction time in efferent nerve (93 M. per sec.)	<u>2.1</u>
Total conduction time	6.5
Central reflex time	3.9

In these determinations the actual rate of conduction was determined in the course of the experiment. Similar values were obtained by Jolly for the central reflex time of the knee jerk. His intervals fell into two groups: one of roughly 2 msec. and one of 4 msec., and he suggested that the first latency involved a more simple reflex arc than the second, *i.e.*, the second had probably one intercalated neuron. Eccles and Sherrington's(1931a)more recent measurements of the flexor reflex indicated a range of values of 2.75 to 4.35 msec. for a single faradic stimulus. *When a second shock is given soon after the first, the central reflex time may be reduced as low as 0.5 msec., but not lower.* The central reflex time is also shortened by increasing the strength of the stimulus, whether it be primary or secondary. The large reduction in central reflex time on the second of two volleys is interpreted as due to "facilitation." For the first response, the stimulus conveyed by the fibres of the dorsal root has to be reinforced by passage through several internuncial cells, there

being a delay of roughly 0.6 msec. at each internuncial cell. If a second volley of impulses follows closely upon a first (which has created subliminal internuncial activity), a motor response is evoked through a shorter chain of internuncial neurons; hence the shortening of the reflex time, even down to 0.5 msec., which is the delay at the synapse in the motoneuron. A greater shortening is obviously impossible as Renshaw (1940) has clearly demonstrated.

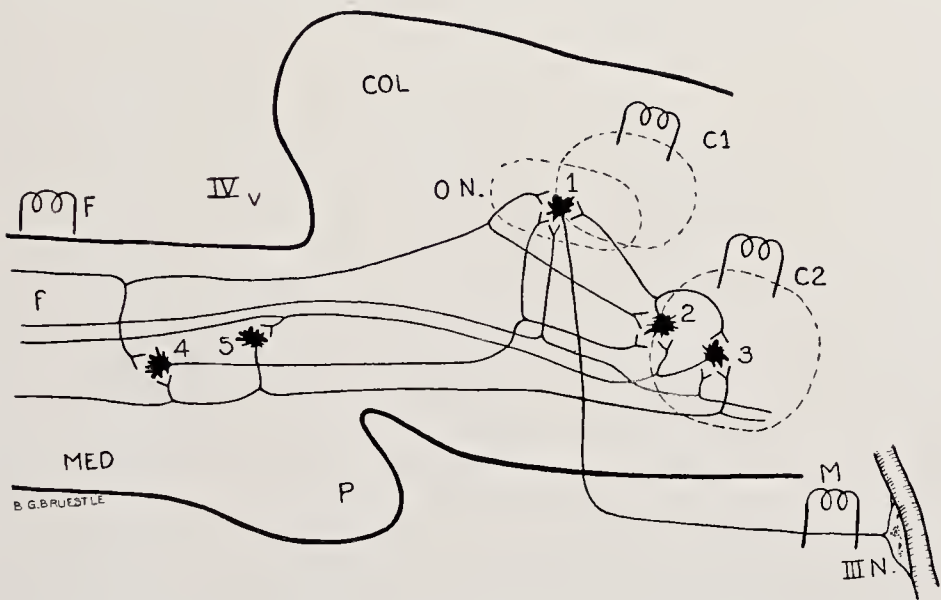


FIG. 20. Diagram illustrating Lorente de Nó's method for determining reflex latency of synapses in third nerve nucleus; COL colliculi, MED medulla, P pons; F, C1, C2 and M positions of the stimulating electrodes; ON oculomotor nucleus, III oculomotor nerve; *f* fibres of longitudinal bundle; 1 motoneurons of third nerve nucleus; 2, 3, 4 and 5 internuncial neurons of reticular substance.

The problem of central reflex time has recently been studied to great advantage by Lorente de Nó (1935abcde&f). He has used the extraocular muscles innervated by the third nerve and has compared the effects of directly stimulating the third nerve nucleus with that of stimulating the posterior longitudinal bundle (fig. 20). He finds that the absolutely refractory period of the motor cells in the third nerve nucleus is no longer than 0.5 msec., and that this value corresponds with the synaptic delay, which in a series of experiments varies from 0.5–0.6 msec. to 0.8–0.9 msec. In this nucleus, the synaptic delay is fairly constant and can be more directly measured than in the case of spinal reflexes.

SUMMATION. The reflex responses evoked by two centripetal volleys

of impulses allow one to study the phenomenon of summation in the central nervous system. Summation is of two types: temporal and spatial.

Temporal summation. When two successive stimuli, each of them too weak to evoke a response, are applied to the same nerve trunk, the second inadequate stimulus may evoke a response if applied at a brief interval (0.1 to 0.5 msec.) (Eccles and Sherrington, 1931b) after the first because of the enduring character of the local excitatory process. Such stimuli may

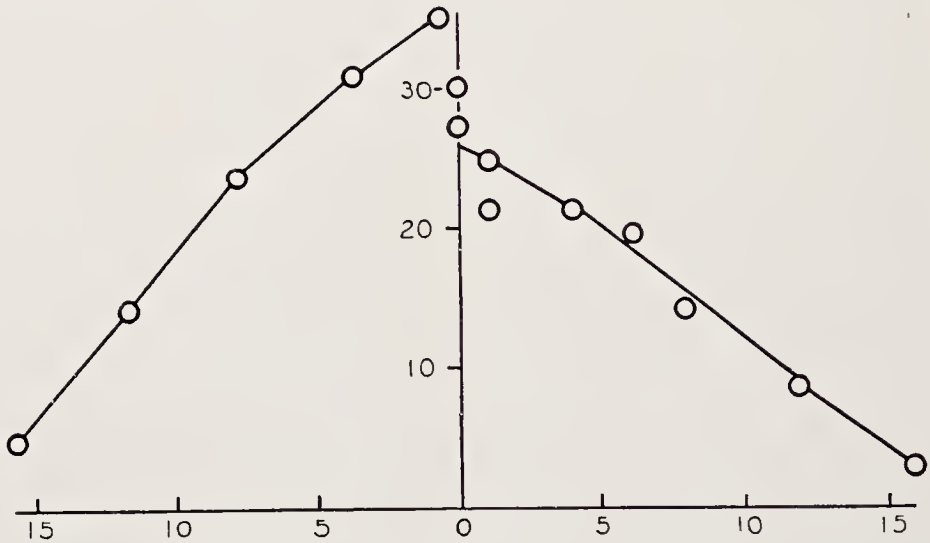


FIG. 21. Reflex responses of tibialis anticus to two threshold stimuli applied to nerves of lateral and medial heads of gastrocnemius at various intervals. Abscissae, stimulus interval in msec.; ordinates, tension in grams. To right of O nerve to a lateral gastrocnemius is stimulated first; to left of O nerve to medial gastrocnemius (Creed, *et al.*, 1932, p. 32).

actually set up a disturbance the spread and size of which is insufficient to excite the nerve further on (Hodgkin, 1937a&b; Katz, 1937). The same phenomenon undoubtedly occurs on the perikaryal surface of nerve cells. Thus in the flexor reflex summation of inadequate stimuli can be demonstrated for 4 to 6 msec., but since this value approaches the relatively refractory period of the afferent nerve fibres it is of doubtful significance. In eye muscle nuclei Lorente de Nó (1935g) finds a maximal summation interval of not more than 0.1 to 0.2 msec. when the neurons are directly stimulated. The part played by temporal summation *at an individual synapse* in the nervous system is thus of theoretical interest only, since the minimum summation interval for inadequate stimuli is as brief as, or briefer than, the refractory period of the afferent nerve fibre.

Spatial summation. Spatial summation, on the other hand, is of primary importance in the physiology of the nervous system. If successive stimuli are applied to two different afferent nerves which play upon the same reflex centre, summated effects can readily be demonstrated. In these circumstances the reflex becomes smaller and smaller the longer the interval between the application of the two shocks. Thus in figure 21 are plotted the reflex responses of tibialis anticus to two just-threshold stimuli applied respectively to the medial and to lateral gastrocnemius nerves of a spinal cat at various intervals; but when the interval exceeds 15 msec., the response virtually disappears. The greatest reaction occurs when the two stimuli are simultaneous. From these observations which have been repeated in other muscles, and by Lorente de Nó in the eye muscles, one may infer that such summation occurs at some focus within the nervous system. Either volley of impulses alone is unable to evoke a reflex discharge, but each creates a change in a number of central neurons which continues in some neurons as long as 15 msec. The second shock, itself inadequate, can in the presence of this excitatory alteration provoke discharge in the neurons thus affected. Sherrington and his various co-workers refer to the excitatory condition set up by an inadequate stimulus as the "central excitatory state," abbreviated *c.e.s.* The term can be used without implication of the nature of the state. Neurons which have been thus affected are also referred to as being in the "subliminal fringe of excitation." Thus Sherrington has conceived of a motoneuron pool (fig. 22), and that an inadequate stimulus from a given nerve, A, produces an enduring subliminal *c.e.s.* in a proportion of the neurons. Nerve B causes similar enhancement of *c.e.s.* in another pool, some of the neurons of which overlap with those affected by nerve A. In these circumstances, the *c.e.s.* of these neurons becomes raised to the threshold of discharge.

Any theory of central excitation must take into account the existence of an enduring *c.e.s.*, lasting from 10 to 20 msec. The delay at the individual central synapses appears to be of the order of 0.5 to perhaps 2 msec. Direct evidence on the duration of the delay at different types of neurons is still lacking, but the figures given by Eccles (1937b) for the superior cervical ganglion (0.5 to 2 msec.) justify the assumption of 2 msec. as the longest delay in the spinal neurons concerned with the production of motor reflexes. Lorente de Nó has shown that in a single central synapse summation of inadequate stimuli can be demonstrated over

an interval not greater than 0.5 msec. He also points out, however, that when internuncial neurons are involved in transmission they may so delay impulses that the final motor neuron is under continuous subliminal excitation for periods up to 10 to 20 msec. Lorente de Nó(1935f)

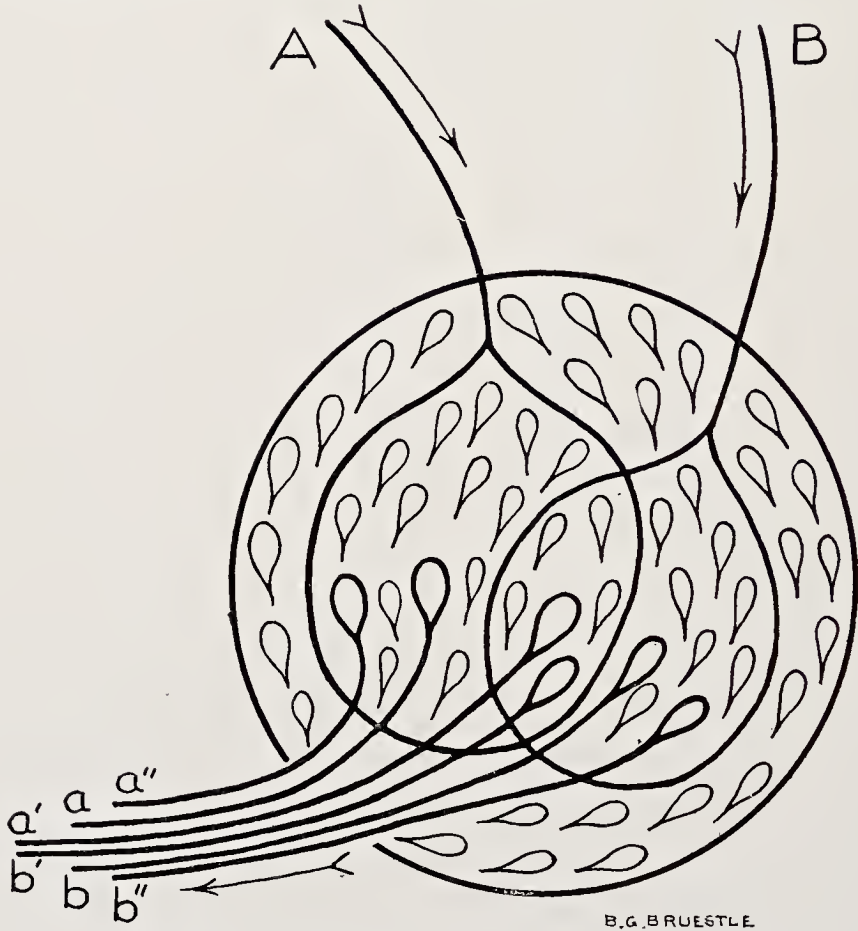


FIG. 22. Diagram illustrating subliminal fringe of excitation. Two excitatory afferents, A and B, with their respective fields of subthreshold excitation indicated in each instance by heavy line. When two neurons are stimulated simultaneously, fields of subthreshold excitation overlap and excitation of these neurons results, *i.e.*, a' and b' , but not of a and b or of a'' and b'' (after Creed, *et al.*, 1932, p. 33).

believes, furthermore, that the enduring character of *c.e.s.*, as demonstrated in the spinal reflex, can be adequately explained by the assumption that several internuncial neurons are intercalated between the sensory fibres and the anterior horn cells. A slight elaboration of this hypothesis can be made to account for other more enduring responses to

single stimuli. Lorente de Nó postulates that if circus excitation occurs in a group of internuncials, as is suggested by the potentials that can be led from the spinal cord during the production of reflex discharges, all forms of enduring reflex discharges may in this way be explained.

An alternative explanation of *c.e.s.* has been suggested by Hughes, McCouch and Stewart(1937) and in more definite form by Eccles (1937b). Eccles describes the excitatory effects at the synapse leading to setting up an impulse as the "detonator" action(1936b); it has brief temporal characteristics, whereas *c.e.s.* which follows a subliminal detonator action has a much slower time course and determines the *threshold* to detonator discharge. An elevated *c.e.s.* may endure in the superior cervical ganglia from 30 to 40 msec. It is therefore possible that in the spinal cord the effect of internuncial discharge is reinforced by production of *c.e.s.*

REFRACTORY PERIOD. As in peripheral nerves, motor neurons and their synapses exhibit a period of recovery, which may be divided into three parts:(i) absolute, (ii) relative, and (iii) the supernormal phase.

Absolutely refractory period. The interval during which a motor neuron is completely inexcitable corresponds roughly with the absolutely refractory period of the axon to which the cell gives rise. The evidence for this is in part indirect. In the first place, one is dealing with a large collection of units and an early second response may represent fresh cells responding rather than a second reaction of the first neuron. This difficulty can to a certain extent be avoided by using intense break-shock stimuli. Denny-Brown(1929a) and Eccles(1931, 1936a) have introduced an ingenious simplification of the experimental situation which involves the use of "antidromic" stimulation. When an uncut motor nerve is stimulated impulses travel backwards up to the ventral horn cells; all these cells are thus set off and the entire group of motor neurons, as a result, becomes simultaneously refractory, as would happen if they had all been caused to discharge at once by a reflex reaction. If, after the application of an antidromic stimulus, the same pool of motor neurons is stimulated at various intervals through an appropriate sensory nerve, the curve of excitability of the motoneuron pool can then be determined. In Eccles' experience the earliest response in the spinal cat occurs at about 5 msec., but since it is impossible by a reflex discharge maximally to stimulate a refractory motoneuron, it is probable that 2.5 msec. is longer than the true refractory period, especially since two antidromic volleys

can be set up within 1 msec. of each other. In the case of the eye muscles, Lorente de N6(1935dfg) has obtained evidence that the absolutely refractory period is actually no longer than 0.5 msec. It should be pointed out, however, that the nerves of the eye muscles are among the most rapid in the body, and the eye muscles themselves the most rapidly acting.

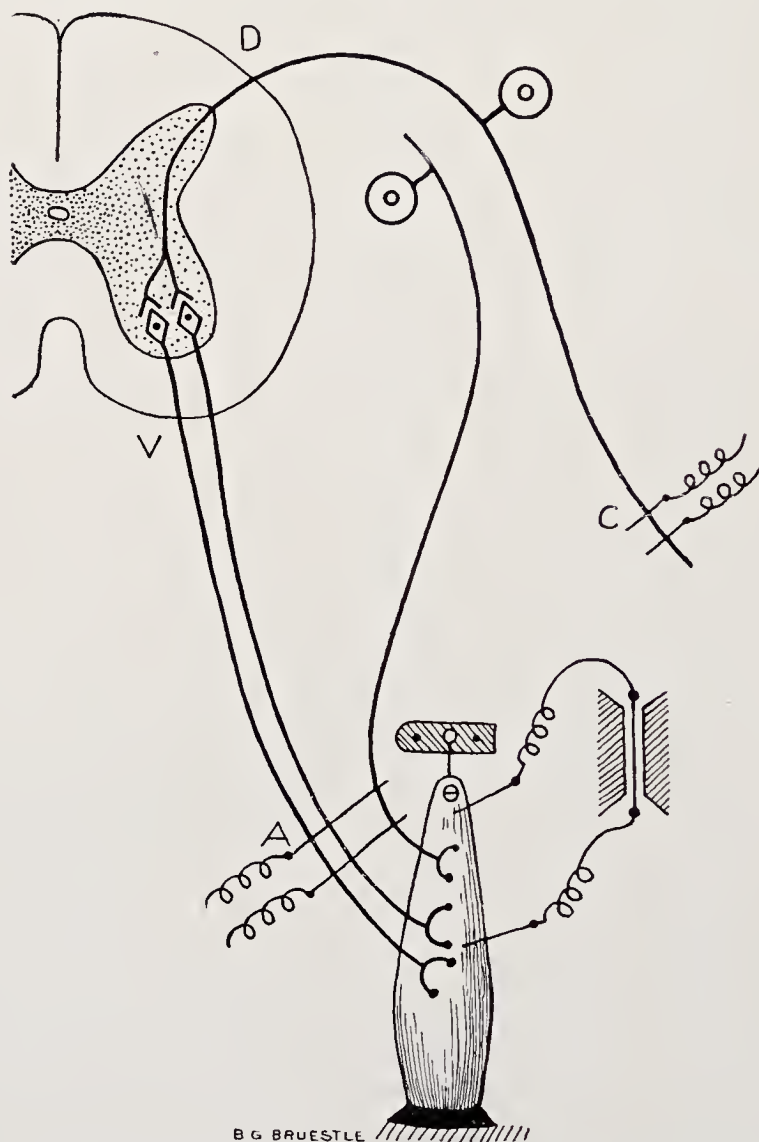


FIG. 23. Antidromic stimulation. Eccles' diagram showing pathways involved in determination of absolutely refractory period of motoneurons by antidromic method. V ventral root. D dorsal root, A electrodes on uncut nerve to muscle, C electrodes on afferent nerve (Eccles, *Proc. roy. Soc.*, 1931, 107B, 557).

Hence one might expect all intervals to be somewhat less in these neurons than in the majority of those to the extremities.

Lloyd(1943)has recently reported that ventral root volleys are followed, after an appropriate interval(essential for nerve conduction in two directions and a brief utilization period), by an antidromic volley in the same ventral root as well as in those of adjacent segments. Since antidromic impulses affect the excitability of ventral root neurons for an appreciable interval(Eccles, 1931), these Lloyd antidromic volleys no doubt play a highly important part in regulating the excitability cycle, inhibitability, and hence the rate of discharge, of neurons in the ventral horn.

Relatively refractory period. Employing the antidromic method, Eccles (1931)has found that the excitability of the motor neurons remains subnormal for a period of about 10 to 15 msec. Lorente de Nó(1935d) found in the eye muscles a relatively refractory period, with the antidromic technique, of 13 to 20 msec. Both Eccles and Lorente de Nó infer that the antidromic stimulus completely removes any preëxisting *c.e.s.* in a motor neuron, but that the interval of refractoriness can be lessened by persistent reflex stimulation of the refractory neurons(rebuilding of *c.e.s.*). The studies of Kleyntjens(1937)in the frog suggest that prolonged antidromic stimulation may differ in its effects from those described in mammals—it appears to facilitate synaptic transmission rather than to induce a refractory state.

Supernormal period. This will be discussed below in relation to the excitability cycle of central neurons.

EXCITABILITY CYCLE OF CENTRAL NEURONS

In peripheral nerves the monophasic action potential is made up of three phases:(i)the familiar “spike,”(ii)the negative after-potential, and (iii)the positive after-potential. During the spike, the nerve is absolutely refractory to further stimulation, but becomes again excitable when the descending phase of the spike is almost completed. Its threshold is high for a certain period of time(relatively refractory period)and the following supernormal period has a time course closely approximating that of the negative after-potential. The size and duration of both varies with the preceding history of the fibre(Gasser, 1935), being increased by mild previous stimulation and, within limits, by a rise of acidity. The positive after-potential also varies with the previous history of the fibre, being increased by previous activity, rise of acidity(Lehmann, 1937), etc. During the positive after-potential, the fibre is less excitable than previ-

ously; since the period falls within the phase of "recovery heat production," the positive potential is evidently generated by the metabolic processes underlying restoration of the fibre.

Action potentials have been obtained from the spinal cord in response to a single volley of impulses applied to a dorsal root fasciculus. The resulting cord potentials are necessarily complicated, since any of the following might contribute to the potential: (i) fibres from the dorsal root, (ii) internuncial neurons, or (iii) the cell bodies and dendrites of the

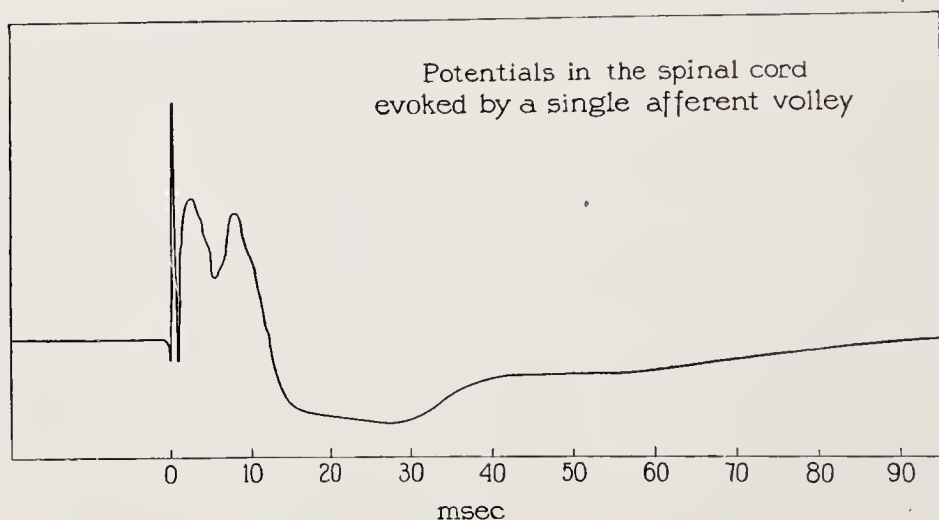


FIG. 24. Action potentials of a cat's spinal cord responding to single break-shock stimulus applied to dorsal root fasciculus (from H. S. Gasser, Harvey Lecture, 1937).

motor cells of the ventral horn. In figure 24 a characteristic cord response is indicated; it consists of three primary elements: (i) an initial spike, (ii) a large and much slower negative potential which is usually double and is sometimes very complex in character, and (iii) a relatively large and prolonged *positive* potential. The secondary negative and positive potentials are large, and they do not correspond in time with the negative and positive after-potentials in peripheral nerves. Gasser (1937) offers the following evidence about the origin of these cord potentials.

The spike potential is clearly a continuation of the spike of the dorsal root fibres. If two dorsal root fasciculi are stimulated separately and then simultaneously, the spike potential represents a simple addition of the two spikes recorded separately. *The secondary negative potentials, however, do not add and are therefore attributable to secondary elements within the spinal cord*, rather than to the negative after-potential of the

dorsal root fibres. These secondary negative potentials might be due in part to the motor horn cells, but when stimulated antidromically a cord potential of this type does not occur, even though antidromic stimuli discharge the entire surface of the ventral horn cell. By process of exclusion Gasser concludes that the potentials following the spike come from the internuncial neurons. The general form of the cord potential is similar to that of the spike potential, but is more spread out, owing to temporal dispersion; the following reasons are given for regarding these negative potentials as asynchronous spike potentials of the internuncials (Erlanger and Gasser, 1937, p. 190). "On account of the short duration of the spike, and the long duration of the positive after-potential, temporal dispersion would curtail the summed height of the spike portions much more than that of the after-potential portion, and thus the large size of the latter in comparison with the former, which is in contrast to the relationship obtaining in records of peripheral A fibres, would in part be accounted for." Gasser further points out that the elements responsible for these negative potentials cannot again be stimulated so long as the potentials endure. Thus when a second shock is applied to a posterior root fibre soon after a first, there is no increase in negative potential.

Further evidence of internuncial origin of these negative potentials comes from study of the reflex response and cord potentials produced by the second of two volleys. If a positive after-potential develops soon after the negative "internuncial" potential of the first stimulus, the response to the second is depressed. *Indeed one can predict from the potentials alone the character of the reflex which will be elicited by the testing volley.* If the after-potential from the first stimulus is primarily negative the response to the testing volley will be augmented — or, to use a more common term, "facilitated" (cf. ch. v).

SYNAPTIC TRANSMISSION *

The more deeply one probes the functions of the central nervous system the more evident it becomes that the two basic problems are those (i) of organization of units and (ii) the nature of the communication between units. Gasser has made the terse remark: "Our knowledge of patterns can never transcend our understanding of a single synapse."

* For material assistance in the preparation of this section I am much indebted to Dr. David Nachmansohn.

The problem of organization is the principal subject of the present volume; the nature of synaptic transmission may now be considered more in detail.

The anatomical structure of the synapse has been described above. The nature of transmission across the synapse and of the forces that inhibit synaptic transmission (ch. v) remains for discussion. The work of Eccles and Sherrington and that of Lorente de Nó indicates that the excitable properties of the central neurons are similar, except for certain minor differences in time relation, to the excitable properties of peripheral nerves, *i.e.*, the axons. Thus, the local excitatory process is of brief duration, both the synaptic delay and the least interval for summation of inadequate stimuli being decidedly shorter than 1 msec. Hence it follows that the local excitatory process set up by any terminal bouton on the surface of an adjacent neuron persists for less than 1 msec. In the case of peripheral nerves, the existence of a polarized interface is generally accepted. When an electrical potential sufficiently disturbs the local ionic distribution of the membrane, a wave of permeability sweeps down the semipermeable surface and this transient change is identified with the nerve impulse. On the basis of present evidence, there is no reason to suppose that the surface of the cell body of any neuron in the nervous system differs essentially from its axon, except in the degree of polarization. The question whether the differences between nerve fibre and synapse conduction are fundamental has been scrutinized by Erlanger (1939). Analyzing some of the peculiarities attributed to the synapse, namely latency, one-way transmission, repetition, temporal summation or facilitation and transmission of the action potential across a nonconducting gap, he points out that all these phenomena can also be demonstrated on fibres. Gasser (1939) arrives at a similar conclusion: The subnormal excitability, *e.g.*, which follows single spikes and trains of spikes and has been first described in nerve fibres by Graham (1935), is characteristic not only of all kinds of axon, but of all parts of the neuron. *He considers the subnormal period as being one of the most important features of nervous activity which the axon has to present for an understanding of the synapse* (ch. v).

These facts make it unnecessary to assume, especially in view of similar time relations, that any condition exists which differs essentially in basic nature from that found in the peripheral axons. The terminal enlargements (bouton) which form in clusters upon the cell bodies are

each one of them capable of forming a local disturbance, presumably developed by their own action potentials: when a sufficient number of such terminals become active on any given cell (*cf.* fig. 18), the cell membrane itself becomes transiently depolarized and the excitation thus inaugurated sweeps down its axon. Insofar as the excitatory process is concerned it is unnecessary to assume the participation of specific chemical substances essential for synaptic transmission different from those essential for conduction.

CHEMICAL MEDIATION. Within the last 20 years, however, there have been proponents of the view that transmission of nerve impulses across synapses occurs by means of "chemical mediation." At first, such an assumption was made to explain the action of the autonomic nerves on their effector organs (Otto Loewi, 1921). If parasympathetic nerves are stimulated acetylcholine is released. This substance, if applied to the effector organ, has an action identical with nerve stimulation. Both effects are paralyzed by atropine. Acetylcholine is normally inactivated by an enzyme which splits the ester into choline and acetic acid. Studies on the nature of this enzyme have revealed its specificity (Easson and Stedman, 1937; Glick, 1938, 1939). The enzyme is called choline esterase. Its action is inhibited by eserine. Injection of eserine into the effector organ produces a prolongation and intensification of the effects of nerve stimulation and of acetylcholine injection. Analogous observations led to the conclusion that the corresponding substance at peripheral sympathetic nerve endings is adrenaline or a related substance, sympathin. The whole subject has been frequently reviewed (O. Loewi, 1933; Bacq, 1935; Rosenbluth, 1937).

The evidence that these substances are the "mediators" of nerve impulses from autonomic nerves to their effector organs appeared very impressive, but when this concept was applied to the central nervous system the evidence proved less satisfactory. It has been based on two lines of reasoning.

(i) The enduring character of the central excitatory state, as well as of the central inhibitory state, has been regarded as indicative of chemical as opposed to electrical transmission at the synapse. The state of enhancement of reflex activity which follows the delivery of a single break-shock may last for several seconds or more, which is out of all proportion to the duration of the local excitatory process (less than 1 msec.). However, in the case of the spinal cord, the duration of facilitation is ordinarily less than 1 sec., and Lorente de Nó has brought forward convincing evidence that facilitation in the spinal cord is explicable on the basis of activation of internuncial neurons and of rotation of activity within inter-

nuncial circuits. Such secondary rotational activation serves to excite ventral horn cells over periods of time compatible with observed facilitation within the nervous system.

(ii) In 1933 Dale and his associates suggested that acetylcholine might be the transmitter across ganglionic synapses, *i.e.*, from neuron to neuron. Later the same theory was proposed for the transmission of impulses from motor nerves to striated muscle. These suggestions were based on experiments of the same kind as in the case of the peripheral autonomic system. The main facts established were: (a) Acetylcholine appears in the venous effluent of the superior cervical ganglion when the preganglionic fibres are stimulated, and in the venous effluent of striated muscle when motor nerves are stimulated. Direct stimulation of denervated muscle does not liberate acetylcholine. (b) Acetylcholine injected in minute amounts stimulates the ganglion and, if suitably applied, provokes a brief asynchronous tetanus of striated muscle. (c) Eserine potentiates the effects of motor nerve stimulation and, under certain conditions, of preganglionic fibres. The potentiation of the muscle response to a nerve impulse is produced by other substances inhibiting choline esterase. The potentiating effect is proportional to their activity *in vitro* as inhibitors of choline esterase. (d) Substances blocking neuromuscular transmission, *e.g.*, curare, also greatly depress the muscle response to injected acetylcholine.

There remained however a great number of difficulties and contradictions which have been reviewed and summarized by Eccles (1938). The chief difficulty in the theory as applied to neuromuscular junctions and across ganglionic synapses is the great rapidity of the process, as was emphasized by Brown, Dale and Feldberg (1936). The peripheral autonomic nerves innervate slowly reacting cells. The effects of their stimulation have a long latency, they rise slowly to a maximum with repeated stimulation of the nerve and they outlast the period of the stimulation. It is easy to conceive such effects as being produced by chemical reactions. Neurons and striated muscle fibres are very quickly reacting cells. The transmission of nerve impulses across ganglionic synapses or at neuromuscular junctions occurs within a few msec. at most. Chemical reactions connected with this transmission must therefore occur with the same rapidity. This time factor is of primary importance and dominates all the aspects of transmission at these junctions. Previous to any suggestion of "chemical mediation" in ganglia and at neuromuscular junctions Adrian had insisted on this point (1933). In his critical review Eccles divides the transmission of nerve impulses into two groups: transmitters of long duration and transmitters of short duration. He attached physiological significance to acetylcholine at neuromuscular junctions and at synapses. He was, however, strongly opposed to a transmitter function of acetylcholine for processes of short duration. His opposition was based mainly on the argument that acetylcholine cannot be removed with sufficient rapidity. According to both proponents and opponents of the theory that acetylcholine is the transmitter substance of nerve impulses across synapses or at neuromuscular junctions it appeared essential to know whether the rate of acetylcholine metabolism is as high as required by the theory of its transmitter function.

No experimental data are yet available which establish the rate of acetylcholine appearance during the period of nerve action. But there are adequate data on the rate at which acetylcholine can be removed

from the sites of action. Studies on the concentration and distribution of choline esterase have revealed that at motor end plates and ganglionic synapses, as well as at synapses of the central nervous system, considerable amounts of acetylcholine can be split in milliseconds. These amounts, if released at such loci, would be high enough for a stimulating action.

Striated muscle. Striated muscle has a surprisingly low concentration of choline esterase. If the enzyme were evenly distributed it would take about 100 sec. in frogs and 300 sec. in mammalian muscle to split at the nerve endings an amount of acetylcholine which would have a stimulating effect. If acetylcholine acts as transmitter it should be removed during the refractory period from the site of its action. The refractory period is about 5 msec. in frogs and 2 msec. in mammalian muscle. The time of hydrolysis by the muscle fibre is therefore about 50,000 times longer than the refractory period (Marnay and Nachmansohn, 1937).

But if, in frog's sartorius, the concentration of choline esterase in the nerveless pelvic end is compared with that in parts containing nerve endings the esterase power is several hundred per cent higher in these latter parts than in the pelvic end (Marnay and Nachmansohn, 1937, 1938). From the figures found for the sciatic nerve it can be calculated that the nerve fibres can not increase the esterase power of the muscle by more than a few per cent. This increase of several hundred per cent can therefore be attributed almost wholly to a high concentration of the enzyme at the nerve endings. This indicates, as the nerve endings occupy not more than $1/1000$ of the whole muscle volume and most probably much less, that the concentration at the nerve endings is many thousand times as high as in the muscle fibre. Since the number of motor end plates in frog's sartorius is known, the absolute amount of acetylcholine which can be hydrolyzed at the nerve endings can be estimated. About 2×10^{-6} μg of acetylcholine can be split at a single nerve ending of a frog's sartorius during the refractory period. This amount corresponds to 8×10^9 molecules of acetylcholine. This is a large amount which, if released at the nerve endings, would certainly have a stimulating effect (Marnay and Nachmansohn, 1938; Nachmansohn, 1939).

Evidence for a high concentration at motor end plates can also be offered for mammalian muscle: in the interior section of the gastrocnemius of guinea-pigs all motor end plates are located at one level only.

The concentration of choline esterase in this part is 6 to 8 times as high as that in a part free from nerve endings. After section of the motor nerve when the degenerated fibres have disappeared the enzyme concentration in the part containing the motor end plates and later the sole plates remains at first practically unchanged and then decreases only slightly (Couteaux and Nachmansohn, 1940).

Sympathetic ganglia. According to the figures available about $2 - 3 \times 10^{11}$ molecules acetylcholine can be liberated by a maximal shock in the superior cervical ganglion of cats. The concentration of choline esterase in this ganglion is high, considerably higher than in the preganglionic fibres. The $QChE$. (mgm. acetylcholine split by 100 mgm. fresh tissue in 60 min.) is about 40–60, whereas it is only 5 in the fibres (Nachmansohn, 1939). If the difference between fibre and ganglion is due to the higher concentration at the region of synapses, from 3–6 mgm. of acetylcholine can be hydrolyzed there during 60 min., or $3 - 6 \times 10^{12}$ molecules acetylcholine during one millisecond. It has been objected that part of that enzyme may be present inside the preganglionic fibres and would therefore not participate in removing the liberated acetylcholine. When the preganglionic fibres are cut, the $QChE$. of the ganglion decreases indeed to 20–25 during the period in which the preganglionic fibres disappear. Only this fraction of the enzyme present at synapses can account for the removal of the liberated acetylcholine. But even this remaining amount of enzyme is high enough to split in 1 msec. an amount of acetylcholine about ten times as high as that liberated by a maximal shock.

Central nervous system. The same enzymatic mechanism exists at central synapses as that described above at motor end plates and ganglionic synapses (Nachmansohn, 1939). In the grey matter which contains the cell bodies and synapses the concentration of choline esterase is always high whereas it is comparatively low in the white matter. Great variations are found in the different parts of the brain. In the ox brain, e.g., the values of $QChE$. are 2–3 in the cortex, 15–20 in the retina, 4 in the posterior quadrigeminal bodies, 10–12 in the anterior quadrigeminal bodies, about 40 in caudate nucleus and 68–69 in the lentiform nucleus (Putamen). The values vary also considerably from one species to the other. The smaller the brain, the higher generally the enzyme concentration. In small animals (rats, rabbits) the values are higher, in human brain lower than those mentioned in the ox brain. The most remarkable

fact about these figures is the great constancy of the values for the same part and the same species, in striking contrast to the variations between the different parts and the different species. The values show moreover that considerable amounts of acetylcholine can be split at central synapses in 1 msec., as at motor end plates and at ganglionic synapses. The very existence of such a specific enzymatic system at all these foci supports the view that the substrate has there the same function. It is in agreement with the generally accepted view that the mechanism of transmission is essentially similar at all synapses (Sherrington, 1906).

Embryological development and choline esterase. If acetylcholine has a role intrinsically connected with transmission of nerve impulses at neuromuscular junctions and at synapses choline esterase should be present in high concentration at a very early stage of development, actually at the time when the first muscular movements occur and the different centers of the central nervous system begin to function. This has been demonstrated in different ways. In the muscle of chick embryos the concentration increases rapidly to high values during incubation (Nachmansohn, 1939). The *QChE.* of breast muscle, *e.g.*, is about 10 at hatching. After hatching the values go down, the *QChE.* of fowl muscle being only 0.4–0.5. These figures offer evidence for a high concentration of the enzyme at motor end plates at a very early stage of development. During the last few days of incubation and at hatching the muscle fibres are extremely small, per unit of tissue weight there is a large number of end plates which are developed at an early stage, and therefore the high values of *QChE.* obviously indicate the high enzyme concentration already present at these foci. Later, when the fibres grow, the number of end plates per unit of weight decreases correspondingly and with it the enzyme concentration. Similar observations were made on rabbit and rat muscle.

In the central nervous system the time when the centers begin to function coincides also with the time when the high concentration of the enzyme appears (Nachmansohn, 1939). In the brain of the chick embryo the *QChE.* rises from 10 at the 16th day of incubation to 20 at hatching; during the first week after hatching it increases further to 25 or 26 which is the same value as in fowl brain. The functions of chicken brain are fairly well developed at hatching. The rapid rise of choline esterase during the last 4 days of incubation is particularly striking when compared with the figures in the brain of young mammals. In the brain of new born rats and rabbits which are markedly undeveloped, the enzyme concentration is very low; during the first 3 weeks after birth the concentration increases rapidly to high values, and that is the time during which the brain functions develop. In the brain of new born guinea-pigs, on the other hand, which are well developed at birth the enzyme concentration is nearly as high as in adults.

The different centers of the central nervous system do not develop at an equal rate. During recent years this problem has been investigated by Barcroft and Barron (1939) in connection with the movements and reflexes of sheep foetuses. Their observations offer evidence for the early development of spinal reflexes and of the relatively delayed period at which the brain enters into action. At first there are local reflexes, later the reticulo-spinal system becomes more and more impor-

tant, and only at a late period the brain takes over the "dominance of the body." The time when the different centres begin to function coincides again with the appearance of a high concentration of choline esterase: This concentration is high in the spinal cord at a very early age of the sheep foetus, but low at that time in the different brain centres where it rises to high values only during the last weeks before birth (Nachmansohn, 1940). Similar observations carried out on human foetus led to the same result (Youngstrom, 1941). Here again a significant relationship was found between choline esterase concentration in some brain centres and developing motility and behaviour.

The facts described so far show that acetylcholine metabolism has about the same rate at the central synapses as in ganglia or neuromuscular junctions, and that the physiological function of the described enzyme system is there the same. Such an assumption is supported by other observations. Some of them appear significant and may be mentioned briefly. Bonnet and Bremer (1937) found a stimulating action of acetylcholine on the activity of cortex and spinal cord. The dose applied was significantly small: $0.1 \mu\text{g}$. The authors see in this fact an indication that a "neurohumoral" factor may determine the rhythmic activity of cortical neurons and the after-discharge of spinal reflexes. Investigating the phenomena of facilitation and the after-discharge Moruzzi comes to the same conclusion (1939). Chang and coworkers have demonstrated that acetylcholine is liberated in central synapses (1938). The pharmacological action of acetylcholine, eserine and related substances on the central nervous system has been tested by several investigators. Effects on the knee jerk were obtained by Schweitzer and Wright (1937, 1938). The interpretation however of such observations has to keep in mind the complex nature of pharmacological actions, which is only relevant if supported by other kind of evidence. Miller, Stavraky and Woonton (1940) demonstrated by use of the electrocorticogram that eserine applied in small amounts to the cortex of cats and rabbits produces changes indicating cortical stimulation. Acetylcholine without eserization evokes similar changes although to a lesser degree. But after eserization the spikes are very powerful and resemble in appearance the strychnine spikes described by Dusser de Barenne and McCulloch. This latter fact is noteworthy in connection with the observation that *strychnine inhibits choline esterase in vitro in concentrations which in vivo are capable of causing convulsions*.

An important and interesting contribution to the problem is the evidence that acetylcholine can be formed by brain slices in vitro. It ap-

appears significant that this formation occurs only with brain slices whereas in all other tissues examined such a formation could not be observed (Mann, Tennenbaum and Quastel, 1938).

ACETYLCHOLINE AND ELECTRICAL THEORY OF TRANSMISSION. The investigations on the concentration of choline esterase described above have shown that the removal of acetylcholine can occur at a rate rapid enough for the assumption that acetylcholine is involved in the transmitter process at synapses. This does however not imply that acetylcholine acts as the specific "synaptic transmitter" of nerve impulses to an effector organ or to a second neuron as originally conceived. Recent investigations suggest that acetylcholine metabolism is closely connected with the electrical changes during nerve activity everywhere at or near the neuronal surface, and is only quantitatively more important at the synapse where the neuronal surface increases. The new conception is based on two lines of evidence (see Fulton and Nachmansohn, 1943).

Choline esterase and electric potentials. A relationship exists between electric potential and activity of choline esterase in the electric organs of fishes. These organs are considered as modified muscle end plates, phylogenetically evolved by transformation of striated muscle. Their discharge does not differ in nature from the action potential of ordinary nerves. It is only the arrangement of the plates in series like in a Voltaic pile by which these organs are distinguished and by which the great E.M.F. is obtained. This was early recognized by the physiologists of the last century. A high concentration of choline esterase exists in the strong electric organs of *Torpedo marmorata*, *Gymnotorpedo occidentalis* (Storer) and *Electrophorus electricus* (Linnaeus). These organs can split in 60 min. an amount of acetylcholine equivalent to 1 to 3 times their own weight or even more. As in the larger specimens the organs have a weight of many kilograms (up to 10 kgm. in the *Gymnotorpedo occidentalis*) the amount of acetylcholine which can be split in these organs may be many kgm. in 60 min., that is in one sec. several mgm. The enzyme concentration is of the same order of magnitude as that estimated for motor end plates. This high rate of metabolism makes possible the assumption that acetylcholine is closely connected with the discharge, as a prerequisite for such a conception is the possibility of a quick removal of the active substance.

Electric organs are highly specialized in their function. The discharge is here the final event. There is no synaptic transmission because there

is no second unit to which the impulse has to be transmitted. The existence of such a high enzyme concentration appears particularly significant in view of the high water (92 per cent) and low protein content (2-3 per cent) of these organs. In the weak electric organ of Ray the enzyme concentration is relatively low. The number of plates per cm. and E.M.F. per cm. in the three species show a parallelism with the concentration of choline esterase. Such a parallelism can also be shown with the electric organ of *Electrophorus electricus*. In this organ great variations of enzyme concentration occur. An S-shaped curve is obtained if the enzyme activity is determined in different sections from the head end to the caudal end of the organ. The shape of the curve is essentially the same as that which indicates the V of the action potential per cm. Moreover, V per cm. and $QChE$. run parallel not only if measured on the same specimen but even if compared in fish of different size and with considerable differences of the E.M.F. of the action potential. The parallelism appears to be so close, even in absolute values, that the enzyme concentration may be predicted from the voltage and vice versa with good approximation (Nachmansohn, Cox, Coates and Machado, 1942).

The significance of this parallelism is emphasized by the fact that it appears to be specific. In contrast to the great variations of choline esterase the rate of respiration is the same in all sections from the head end to the caudal end of the organ. Even between the strong main organ and the weak "bundle of Sachs" there is no measurable difference. Nerve activity is connected with heat production and extra oxygen uptake. Oxidation is however a slow process. In the electric organ, as in nerve, the rate of respiration is particularly low. Although it certainly is — as for all cellular functions — the ultimate source of energy required for conduction, other chemical reactions must be more immediately connected with the action potential. At least 5,000 to 10,000 more molecules of ACh. (probably the estimate is much too low) can be split per unit of time and per unit of electric tissue, than molecules of oxygen can be taken up. The high metabolic rate of acetylcholine, although being a necessary prerequisite, would in itself not be sufficient support for the assumption of a direct relationship with the action potential. But in connection with the apparently specific parallelism found between choline esterase concentration and the E.M.F. of the discharge it becomes pertinent. Other enzymes and substances examined, *e.g.* phos-

phorylated compounds, which are also of consequence during nerve activity, are evenly distributed throughout the organ.

The assumption that the discharge is connected with acetylcholine metabolism is further supported by the fact that during stimulation acetylcholine appears in the perfusion fluid provided that choline esterase has been inactivated by eserine. Injection of small amounts of acetylcholine into the organ produces a discharge which is greatly enhanced by eserine (Feldberg, Fessard and Nachmansohn, 1940).

Localization of choline esterase. The second line of evidence leading to a modification of the original theories is the localization of the enzyme inside the nerve cell. The concentration of choline esterase is high in all nerve fibers, but rises still more at synaptic regions. This is particularly obvious in nonmyelinated fibers. In the abdominal chain of lobsters the *QChE.* values are as high as 5-15, and rise at the points where the synapses are located to values of 18-30. In the sympathetic chain of mammals the differences between trunk and synaptic regions are similar. Between myelinated fibers and grey matter the differences are somewhat greater, but in principle there is always only a quantitative difference. Furthermore, Lorente de N6 (1938) has shown that acetylcholine is released by ganglion cells after impulses have passed in which no synaptic transmission is involved and in peripheral nerves. This has been confirmed by Lissák (1939). These facts indicate that acetylcholine metabolism is not limited to nerve endings. The experiments mentioned above on the superior cervical ganglion of cats after section of the preganglionic fibres suggested that the difference in enzyme concentration between fibre and synapse may be connected, partly at least, with the difference of surface extension. It could be calculated from these experiments that the enzyme concentration in the preganglionic fibre is several times as high inside the ganglion as in the same fibre before it enters the ganglion. This increase was interpreted as being connected with the increase of surface due to the extensive end arborisation of the preganglionic fibres in the ganglion. Evidence for this view has been offered with the giant fibre of squids: choline esterase is localized practically completely in the sheath. In the axoplasm the enzyme activity is negligible (Boell and Nachmansohn, 1940).

As in the case of the parallelism found between choline esterase concentration and E.M.F. of the action potential the localization of the enzyme at the neuronal surface can be considered as being significant, if

it is specific. Studies on the distribution in the nerve cell of enzymes and coenzymes possibly of consequence during activity have been initiated. It has been found that, in contrast to choline esterase, the greatest part of cytochrome oxidase is localized in the axoplasm (Nachmansohn, Steinbach, Machado and Spiegelman, 1943). Succinic dehydrogenase widely considered as an important link in respiration has a similar distribution as cytochrome oxidase (Nachmansohn and Steinbach, 1942). The observations indicate that the bulk of the respiratory enzyme systems is located in the axoplasm. This is consistent with the fact that the energy required for activity, as indicated by the heat production and extra oxygen uptake, is small.

Another catalyst studied was vitamin B₁ as diphosphothiamin which may be important for the synthesis of acetylcholine (Mann and Quastel, 1940). This coenzyme is concentrated in the sheath many times as high as in the axioplasm. It is possible that an important factor in the sensitiveness of nervous tissue to vitamin B₁ deficiency is the decrease of the rate of acetylcholine formation.

Bioelectrical phenomena occur at the surface. The peculiar localization of choline esterase appears particularly pertinent in connection with the close relationship between the enzyme concentration and the E.M.F. of the action potential, and the large amounts of acetylcholine which can be metabolized in milliseconds. Moreover, if it is recalled that acetylcholine generates potential changes in significantly small amounts and that eserine greatly enhances this effect, the evidence appears impressive. Every single fact alone would not be sufficient support, but considering them all together the conclusion is justified that acetylcholine metabolism is intrinsically connected with the electrical changes during nerve activity at the neuronal surface and is not limited to nerve endings. There it is only quantitatively more important owing to the increase of surface. As outlined above the electrical signs of nerve activity do not support the assumption that the mechanism of transmission of nerve impulses across synapses differs fundamentally from that by which impulses are conducted along the fibre. The new concept removes the chief difficulty for conciliating "electrical" and "chemical" theory of transmission of nerve impulses for it makes it unnecessary to assume a basic difference of the role of ACh for conduction of nerve impulses along fibres and across synapses. If the release, the action and the inactivation of acetylcholine follow a temporal course comparable to that of the action current of the nerve impulse — and the recent results sug-

gest such a course — then the difference between chemical and electrical transmission is, as Lorente de N6 said in the *Symposium on the synapse*, a pure formality.

The resynthesis of acetylcholine requires energy. Energy-rich phosphate bonds are considered to be the most readily available source of energy for endogenous life processes. In muscle the release of phosphate from adenosinetriphosphate seems to be the primary source of the contraction energy (Meyerhof, 1941) and possibly directly connected with the mechanical change during the contraction (Engelhardt, 1942). The adenosinephosphate is rapidly phosphorylated by the breakdown of phosphocreatine, a substance in which the phosphate bond is also rich in energy, the breakdown of one mole of phosphocreatine into creatine and phosphoric acid yielding about 10,000 g calories. The phosphocreatine thus acts as a "storehouse" or an "accumulator" for the energy of phosphate bonds (Lipmann, 1941). The presence of phosphocreatine in nerve suggests that there too its phosphate bond is the storehouse for the energy of the action potential, adenosinetriphosphate acting as catalyst. In ordinary nerve, however, it is difficult to compare the energy output of the action potential with the energy released by the breakdown of phosphocreatine and only some general estimates are possible. In the electric organ both electrical and chemical changes are within the range of possible measurement. Such experiments were recently carried out on the electric organ of *Electrophorus electricus* (Nachmansohn, Cox, Coates and Machado, 1943). The electrical energy released externally by 1,600 discharges was about 5–6 g calories in a section 10 cm. long containing about 350–400 g of electric tissue. The energy released by the breakdown of phosphocreatine during the same period was on the average between 20 and 30 g calories. The breakdown of phosphocreatine is therefore adequate to account for the energy produced by the action potential. The total heat production of 1 gm. of crab nerve during one impulse is 35×10^{-6} g calories. For 400 gm. of nerve and 1,600 impulses this would correspond to about 22 g calories. Thus the total heat production seems to be close to the amount of energy released by the phosphocreatine breakdown. The amounts of acetylcholine and phosphocreatine metabolized are of the same order of magnitude. It thus appears probable that the phosphate bond energy is the main energy source for the formation of acetylcholine.

Other chemical reactions may be and probably are involved. The work

of Bronk and his associates indicates the importance of different factors in the surrounding medium(1939). Changes in ion concentration have strong effects on the degree of activity, potassium increasing, calcium depressing it. The importance of oxidative processes has been mentioned above. Asphyxia leads within the course of about 10 minutes to a decrease in the postganglionic discharge. The response to chemical stimuli and to presynaptic impulses is abolished at about the same time. This parallel time course of failure for chemical or synaptic excitation suggests that the irritability of the cell fails as soon as any part of the synaptic mechanism. Asphyxia blocks not only transmission across synapses but also simultaneously conduction over those preganglionic fibres which course uninterruptedly through the ganglion. Bronk and his associates were surprised to find this identical time course of failure and inferred from this that the processes involved in synaptic transmission are not more susceptible to lack of oxygen than are those responsible for conduction over certain axons. In the light of the recent development these conclusions appear well justified and find a satisfactory explanation.

The relationship between the intensity of the discharge and acetylcholine metabolism does not imply that acetylcholine produces the E.M.F. directly by action on the surface. Cole and Curtis(1939) have shown by alternating current impedance measurements that the action potentials are associated with a transient change in resistance. Both resistance and E.M.F. are closely associated properties of the membrane and their sudden changes are responsible for the initiation and propagation of the nerve impulse. It is well conceivable that the E.M.F. is mainly due to the difference in ion concentration inside and outside the fibre and that acetylcholine decreases the resistance by action on the membrane surface, although Beutner and Barnes(1941) have described a model where acetylcholine has a much stronger electromotive force than any other substance tried. A substance which can appear and disappear within a millisecond could well account for the transient changes occurring at the surface. Such an idea would be well compatible with the concept of propagated impulses developed originally by Keith Lucas (1917) and Adrian.

SUMMARY

The simplest reaction of the nervous system is the segmental spinal reflex involving two elements, an afferent neuron and a motor unit. The connections of most afferent neurons, however, are such that each may excite motor units of several spinal segments. The simplest reflex reactions are patterns of movement rather than contractions of specific muscles.

The junction between one neuron and another in the nervous system is termed a "synapse." The prevailing type of synapse throughout the nervous system is the terminal knob or bouton (figs. 18 and 19); a single neuron may be surrounded by many hundreds of such synaptic unions. When an axon is severed, the first structural change in the subsequent degeneration is found in the enlarged terminals to which the axon gives rise. They first swell and after three days granulate, fragment and ultimately disappear *without affecting the structure of the cell on which they terminate* (neuron doctrine).

When one cell activates another in the nervous system, its impulse must pass across the synapse. This requires a measurable time interval which for most synapses in the mammalian spinal cord amounts to 0.5 to 1.0 msec. The normal reflex latency is made up of a number of synaptic delays at the neurons successively activated by the impulses on their way to the motoneurons.

A discharge at a *single* axon terminal may be insufficient to excite a ventral horn cell. Repetitive discharge of such terminals might suffice to stimulate a motor horn cell, but since the least interval for summation of inadequate stimuli in the motoneuron is less than the refractory period of the afferent neuron, it is now generally believed that *temporal summation* of this type plays no important part in synaptic transmission (Lorente de Nó). *Spatial summation*, however, is of primary importance; thus if activation from one axon terminal fails to excite, simultaneous activity of several such terminals on the same neuron may cause it to discharge. This presupposes that the local excitatory process set up by a single ending travels an appreciable distance along the surface of the cell so as to summate with the corresponding process of other endings.

There is no evidence that synaptic transmission of nerve impulses differs fundamentally from conduction along fibres. Recent investiga-

tions suggest that the concept of acetylcholine as a "synaptic transmitter" in its original form has to be abandoned. The release of acetylcholine appears to be intrinsically connected with the nerve action potential, thus playing an essential role in the mechanism of conduction of nerve impulses along fibres as well as across synapses.

The neurons of the spinal cord exhibit spike potentials as well as positive and negative potentials similar to those of the peripheral axons. A large negative potential following the spike is associated with states of increased excitability probably of internuncial neurons. A large positive potential accompanies states of depressed excitability. From the characteristics of the cord potential one can predict the character of the reflex response.

Central neurons also have refractory periods similar to those of peripheral axons, the absolutely refractory period of ventral horn cells being of the order of 1 to 2 msec. or less, and the relatively refractory period 10 to 15 msec.

V

CENTRAL INHIBITION *

HISTORICAL NOTE

The concept of inhibition as applied to the central nervous system crystallized slowly, but it undoubtedly had its origin in the rediscovery by the brothers Weber (1845) that stimulation of the peripheral end of the vagus nerve causes temporary cessation of the heart beat. The observation had also been made previously by Volkmann (1838) and there were other instances of vagal stimulation prior to the Webers (H. E. Hoff, 1936). The Webers, however, were the first to see the wider implications of the fact that excitation of a nerve could cause arrest of activity of an innervated tissue. Pflüger (1865) made a systematic investigation of inhibitory nerves (belonging principally to the autonomic system), finding that intestinal movements may be inhibited by stimulation of the splanchnic nerve. In 1863, Goltz had reported that the heart could be reflexly inhibited in the frog by tapping on the stomach (*Klopfversuch*).

These investigations precipitated a search for inhibitory nerves to skeletal muscles. Pavlov (1885) found an inhibitory nerve passing to the adductor muscle of the bivalve *Anodon*, and similar fibres were isolated in the nerves of the claw of the crayfish *Astacus* (Biedermann, 1887). However, no one has found an inhibitory nerve for the skeletal muscle of vertebrates. Hence, inhibition must be a central process, and as far as skeletal muscle is concerned inhibition means mere cessation of activity. If a motor nerve could be instantaneously severed without stimulation, its status would be precisely similar to that of having its ventral horn cells inhibited centrally.

ONE of the most dramatic experiments in Physiology is the inhibition of the crossed extensor reflex. When a fully isolated quadriceps muscle of a decerebrate cat is attached to a myograph, stimulation of the opposite femoral nerve gives rise to the familiar crossed extensor reflex (ch. vii). If during the height of this reaction the sciatic or some smaller nerve on the same side is stimulated, the myograph lever drops dead-beat to the original tension of rest, exactly as if the motor nerve had been instantaneously severed. The latency of the inhibition is little more than the duration of twitch contraction of the muscle itself. By measuring the duration of contraction persisting after application of the inhibitory stimulus, Denny-Brown (1929b) was able to distinguish the red from the white fibre components of certain extensor reflexes, since the red fibres,

* I am much indebted to Dr. David P. C. Lloyd for assistance in the revision of this chapter. — J.F.F.

when nerve impulses are completely cut off, maintain tension for a greater period than do those of the white fibres. In studying the inhibition of the cat's knee jerk it was found when the tap to the patellar tendon and the inhibitory shock were delivered synchronously that the inhibitory stimulus was nevertheless effective ("direct" inhibition, see Lloyd, 1941, 1943c). These facts are mentioned to emphasize the prompt-

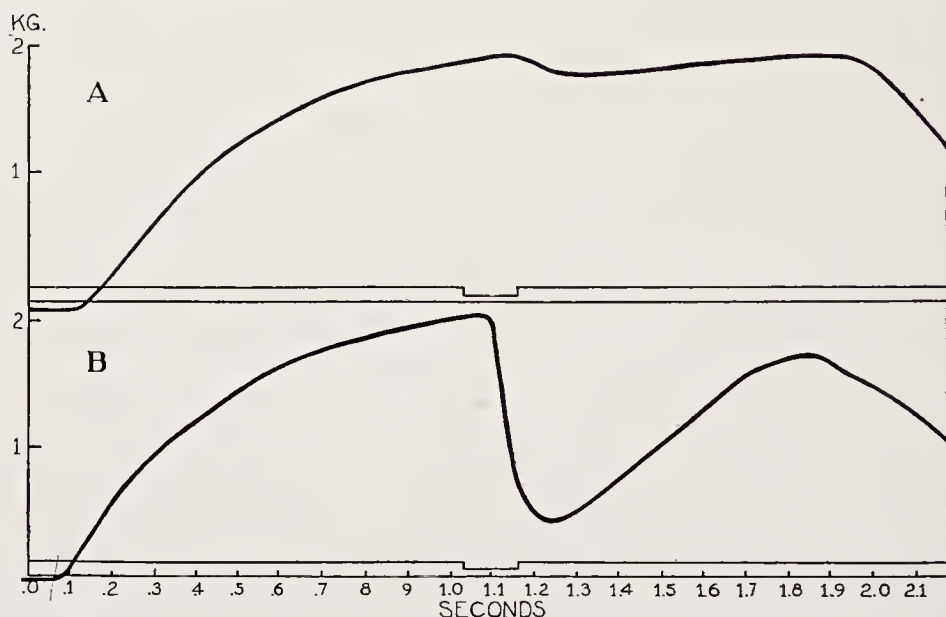


FIG. 25. Crossed extensor reflex of decerebrate cat; quadriceps muscle responding to stimulus applied to peroneopopliteal nerve at 48 per sec. A, Three stimuli dropped during the height of the response. Note slight dip in the plateau. B, Three stimuli applied to ipsilateral inhibitory nerve at height of reflex. Note prompt inhibition of tension (Liddell and Sherrington, *Proc. roy. Soc.*, 1923, 95B, Plate 8).

ness of inhibitory reactions. Emphasis should also be laid upon the enduring character of these inhibitory depressions. Other details may now be given concerning the behaviour of the central inhibitory process itself.

It is clear in the first place that mere cessation of *sensory* stimulation does not cause inhibition. Thus in a crossed extensor reflex cessation for 0.3 sec. of afferent stimulation at the height of a reflex response causes little or no change in the tension curve, whereas a stimulus of this duration delivered to an inhibitory nerve quickly brings the myograph lever toward zero tension (fig. 25). It is evident from observations such as these that central inhibition operates at some point further "down-stream" in the reflex arc than the terminal fibres of the dorsal root, and

also at a point further along than the mechanism causing after discharge. In view of the time relations of the inhibitory process already alluded to, it is likely that the primary seat of inhibition lies either in the ventral horn cells or in the next adjacent internuncial neuron. Recently Renshaw (1941) and Lloyd (1941) have proved that direct inhibition of ventral horn cells may occur in a two-neuron reflex (see below, p. 87).

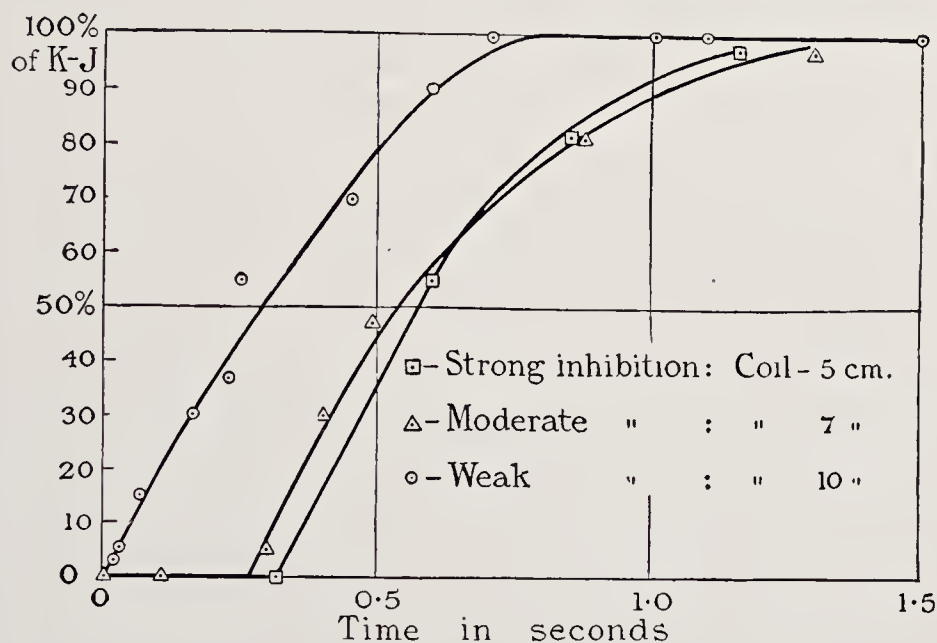


FIG. 26. Recovery curves of knee jerk of spinal animal after single inhibitory break-shock applied to ipsilateral sciatic nerve. Note that a strong break-shock produces a more enduring depression of jerk than a weaker shock (from Ballif, Fulton and Liddell, *Proc. roy. Soc.*, 1925, 98B, p. 599).

INHIBITION OF KNEE JERK. The knee jerk has served as a particularly convenient index of the central inhibitory state (*c.i.s.*). Sherrington (1893) first showed that the spinal knee jerk was an inhibitable phenomenon, and thus established the reaction as a genuine reflex. He also observed that the duration of inhibitory effect considerably outlasted the electrical stimulus which produced it. In their study of the temporal characteristics of the inhibitory process, Ballif, Fulton and Liddell (1925) used a single break-shock as the inhibitory stimulus. Knee jerks were evoked at approximately 3 per sec. and the inhibitory break-shock stimulus was applied at random intervals before and after the tendon tap. The size of the jerk was then plotted against time (fig. 26). The susceptibility to in-

hibition proved far greater in the spinal state than in the decerebrate preparation.

Spinal knee jerk. In the spinal animal, a single break-shock stimulus applied during a series of knee jerks recurring at 3 per sec. may cause complete inhibition of as many as 1 to 5 successive jerks (fig. 27). Following complete inhibition there is a period of partial recovery during which the size of successive jerks is subnormal, *i.e.*, a proportion of the motoneurons are still refractory to stimulation. The duration of inhibition increases with the strength of stimulation (fig. 26). Other things being equal, the greater the strength, the more enduring the inhibition. With a weak stimulus, complete inhibition of the jerk occurred only when the

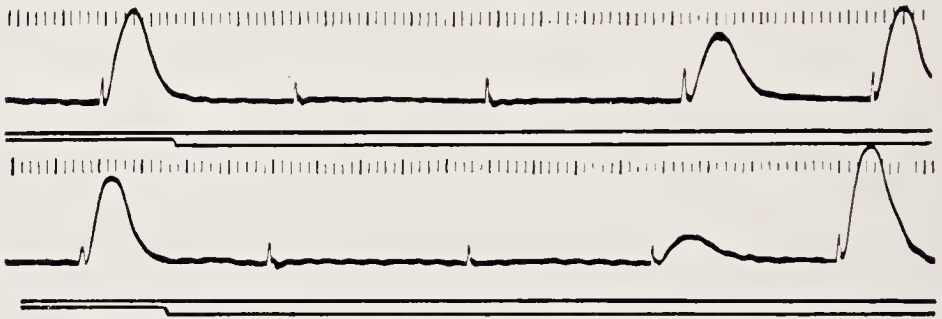


FIG. 27. Knee jerks of spinal preparation delivered at 3 per sec. showing complete inhibition of jerks for period of 1 sec., as a result of application of single break-shock stimulus. Time above: 0.02 sec. (Ballif, Fulton and Liddell, *Proc. roy. Soc.*, 1925, 98B, p. 598).

stimulus and the tendon tap fell simultaneously. With stronger stimuli the period of complete inhibition lasted generally about 1 sec. in the spinal preparation, although in certain animals it might endure for nearly 2 sec.

Decerebrate knee jerk. When a series of jerks is obtained from the patellar tendon of a decerebrate preparation and an inhibitory break-shock applied as above, the threshold of inhibition is found to be much higher and the duration of inhibitory effect more transient than in the spinal condition. The inhibitory stimulus is most effective when it occurs synchronously with the tendon tap. In several instances, inhibition actually occurred when the stimulus was applied 1 to 2 msec. after the tap. The latency of the inhibitory effect is thus surprisingly brief, but the duration of inhibition is also much less than in the spinal state. The period of complete inhibition of the decerebrate knee jerk was generally not greater than 10 msec. and ordinarily it was considerably less.

OTHER FEATURES OF CENTRAL INHIBITORY PROCESS. Comparison of the rate of relaxation of a motor nerve tetanus with the speed of relaxation of the same muscle inhibited during a crossed extensor reflex reveals that the two curves are approximately identical. In other words, the inhibitory process is capable of arresting all motoneurons with approximate simultaneity. When single break-shock stimuli are applied at various intervals

in the course of a crossed extensor reflex, it is found that the reaction is more vulnerable to inhibition toward the end of the response than at the beginning; thus during the stimulation plateau of a crossed extensor reflex a single break-shock may produce only a slight dip in the tension record, whereas if the stimulus is applied during the after-discharge plateau while the tension is unchanged, it may cause an immediate and virtually complete inhibition. The same motoneurons are in operation so long as the tension remains constant in such a reflex; hence one must infer that the same motoneuron is more difficult to inhibit at one time than at another. When weak inhibitory stimuli are applied, relaxation may be gradual, one motoneuron after another dropping out in sequence. Such a phenomenon is referred to as "inhibitory recruitment," a phenomenon entirely similar to that of "excitatory recruitment" which is so conspicuous a feature of the onset of crossed extensor reflexes (Liddell and Sherrington, 1925b).

When the crossed extensor reflex is evoked by a stimulus of known rate, the rhythm of stimulation is not evident in the reflex response. However, if a weak inhibitory stimulus is applied during such a crossed extensor reflex, the rhythm of the excitatory reaction, *e.g.*, 25 per sec., generally becomes evident. This is due to the fact that after discharge is more vulnerable to inhibition than the primary discharges evoked by the individual excitatory stimuli. A weak inhibitory stimulus thus uncovers "a smothered excitatory rhythm" by suppressing the tendency to after discharge (Fulton and Liddell, 1925).

THEORIES OF INHIBITION

In discussing theories of central inhibition Gasser (1937) remarked: "The large number and the diversity of the theories about the nature of inhibition in the nervous system may be taken as a measure of the obscurity which has surrounded the subject. Some of the theories are hardly more than restatements in other terms of the fact that the neurons are inhibited. Others are fabricated in analogy with conditions making for unresponsiveness in other situations. A humoral agent is often postulated, but no such agent has been found; nor is there any evidence for two kinds of fibers, the excitatory and inhibitory, nor for two types of endings of one type of fiber. The Wedensky mechanism and anodal polarization are also not infrequently mentioned. In every instance, the suggestions can neither be accepted nor rejected."

The inadequacy of the Wedensky theory of interference of impulses has often been pointed out. The inadequacy of the humoral theory of inhibition is less obvious. The humoral theory is based largely upon analogy with the peripheral parasympathetic system. The enduring character of the central inhibitory process has been the strongest argument in favour of liberation of a depressant substance in or about the ventral horn cells and internuncial neurons; the duration of the depression was believed to represent the time required for the inhibitory substance to diffuse away from the neurons. This view, like that of the humoral theory of excitation, has served admirably as a working hypothesis, but since no positive evidence has been secured of an active inhibitory substance in the central nervous system, it remains a gratuitous assumption, and it becomes necessary to inquire whether other phenomena recently demonstrated may not be correlated more suitably with central inhibition.

CATEGORIES OF CENTRAL INHIBITION. During the last ten years investigation has turned from an analysis of the reactions of peripheral effectors to the study, by direct methods, of the reactions of nerves, nerve roots, and of the spinal cord itself. Attention has been focussed on the precise timing of central events during the course of reflex action. As a result of these studies, it has become apparent that the phenomena collectively known as central inhibition fall into two or more distinct categories according to mechanism. In one category belong the examples of central inhibition, which are susceptible of explanation on the basis of the subnormal period of recovery in nerve first discovered by Helen T. Graham(1935). In another are those examples of central inhibition which, by recent documentation, cannot be so explained. These broad categories may be referred to as "indirect" and "direct" inhibition, respectively.

Indirect inhibition. Inhibition by intervention of the subnormal period is best exemplified by the flexor reflex. Eccles and Sherrington(1931) demonstrated that the flexor reflex to the second of two single-shock stimuli in successive combination is depressed unless the second shock succeeds the first by an interval greater than 120 msec.(fig. 28). Under similar conditions of afferent excitation, Hughes and Gasser(1934) showed that the negative cord potential, signalling the activity of interneurons, and the reflex discharge to the second of two volleys are decreased in a parallel manner along a time course which follows that of the positive cord potential resulting from the first volley of the pair. Accordingly one need not look for other than the known recovery process of nerve tissue to account for the inhibition of the flexor reflex(Gasser, 1937). A group of motoneurons, after synchronous discharge, has been found to exhibit a prolonged period of subnormality(Lorente de Nó,

1935d), which is sufficient to explain the silent period following the transmission of a tendon jerk reflex. The mechanism for attaining high degrees of unresponsiveness is revealed in the phenomenon of summation of subnormality described by Gasser(1935). An important consideration for the occurrence of inhibition by the intervention of subnormality lies

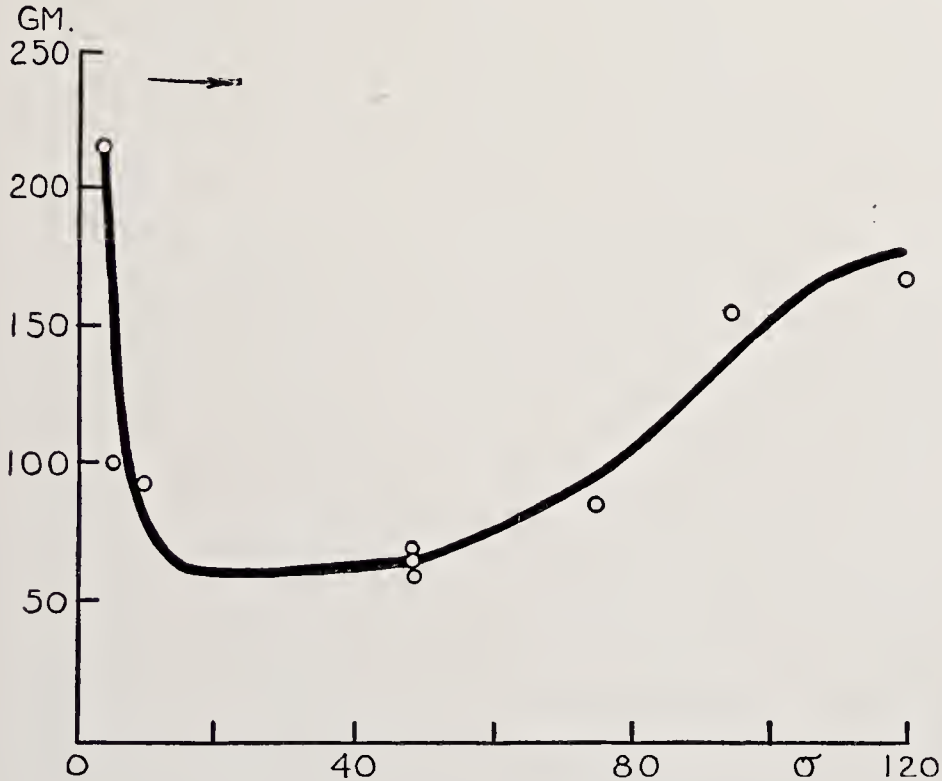


FIG. 28. Flexion reflex of m. tibialis anticus showing depression of response to second of two break-shock stimuli applied to popliteal nerve of decerebrate cat. First stimulus is weaker than second. Tension developed in reflex elicited by second stimulus alone is indicated by arrow (Eccles and Sherrington, *Proc. roy. Soc.*, 1931, 107B, p. 548).

in the necessity for other than synchronous convergence of interacting volleys, which event would lead to summation.

*Direct inhibition.** Several examples of direct inhibition have been recently discovered (Renshaw, 1941, 1942; Lloyd, 1941, 1943a). In each case the condition for the onset of inhibition was simultaneous convergence of the interacting volleys. A single afferent volley in the sixth lumbar dorsal root was found to inhibit the two-neuron-arc reflex discharge

* For a more detailed discussion cf. Lloyd(1943c).

evoked in the first sacral ventral root by a single volley in the first sacral dorsal root, when the two dorsal root volleys were synchronized (Lloyd, 1941). The afferent fibres yielding direct inhibition and excitation of the two-neuron-arc reflex discharge are indistinguishable and belong to the group of large, low-threshold afferent fibres arising in muscle (Lloyd, 1943a). This group of afferent fibres is now known to mediate the tendon jerk reflex, which appears to be made up solely of discharges through arcs of two neurons (Lloyd, 1943b). From examples of direct inhibition at present known it appears that the low-threshold afferent fibres from a given muscle mediate two-neuron-arc excitation to that muscle and inhibition to the motoneurons of neighboring muscles. These experiments show that the direct inhibitory action of muscle afferent fibres accounts for the silent period shown by Denny-Brown (1928) to occur in the gastrocnemius muscle as the reflex accompaniment of the tendon jerk in the quadriceps muscle. Thus, in the case of the tendon jerk, both known forms of inhibition occur together, the indirect inhibition being confined to the motoneurons of the stretched muscle, the direct inhibition having a wider field of action.

An interesting example of direct inhibitory action is found in the demonstration that activity of some motoneurons (obtained by stimulation of their axons) may depress the response of neighboring motoneurons to reflex activation (Renshaw, 1941). The depressant action is particularly effective when the discharging and inhibited motoneurons belong to the same muscle. This fact seemingly accounts for the observation first made by Sherrington (1907b) that stimulation of one of several nerve branches to a muscle (after distal section) inhibits the innervated remainder of that muscle. In this experiment, the motor axons as well as the afferent fibres unavoidably are stimulated, and the resulting impulses in the motor axons, sweeping into the central parts of the motoneurons would have the action just described. It is germane to inquire whether this motoneuron antagonism may be extended to account for inhibition by primary afferent fibres. Since inhibition and two-neuron-arc excitation occur in parallel, one might suppose that motoneurons discharging in the immediate neighborhood of those which are inhibited could in effect exert that inhibitory action. This view is not tenable for inhibition by primary afferent fibres occurs with threshold conditioning shocks, which yield volleys much smaller than the minimum required to secure motoneuron discharge (Lloyd, 1943a).

The mechanism of direct inhibition is not known, nor indeed do we know whether there be one or more mechanisms to account for individual examples of direct central inhibition. Many mechanisms have been urged at one time or another to account for inhibition, and with direct inhibition by synchronous convergence now an established fact, many of these undoubtedly will be revived. The most satisfactory proposal would seem to be that which ascribes direct inhibition to polarization, by the extrinsic field of active neurons, of adjacent neurons essential to the transmission of the reflex which is inhibited (Grundfest, 1940; Renshaw, 1941).

SUMMARY

Inferences concerning inhibition are based upon the reactions of peripheral effectors, particularly skeletal muscles. Since in warm blooded animals there are no inhibitory nerves to skeletal muscle, inhibition may be regarded as a purely central process. Any theory of central inhibition must take into consideration the time relations of inhibition: its brief latency and its enduring character.

In the spinal animal a single break-shock applied to an ipsilateral nerve may completely depress the knee jerk for a period of several seconds; the greater the intensity of the stimulus the longer the period of complete inhibition. The knee jerk of a decerebrate preparation, however, is many times more difficult to inhibit than that of the spinal animal.

When crossed extensor reflexes are subjected to inhibition, the inhibitory effect of the first stimulus may be so prompt that the muscle attains full relaxation in a period scarcely longer than that of a motor nerve twitch.

After-discharge is more susceptible to inhibition than the tension maintained during actual reflex stimulation.

In considering the theories of inhibition, it is pointed out that the interference and the humoral concepts have outlived their usefulness, and that the discovery by Graham of the period of subnormal responses in nerves has thrown fresh light upon the central inhibitory process. Gasser's study of cord potentials has indicated that periods of subnormal responsiveness coincide, as in the case of peripheral nerves, with the period of positive potential. Gasser believes that through internuncial circuits neurons essential for given reflexes are rendered subnormally

responsive, and that this may account for certain types of reflex inhibition.

Such a concept calls upon no postulates which do not find a parallel in a peripheral nerve. The theory does not exclude the possibility of some humoral agent being responsible for states of subnormal responsiveness, but until positive evidence is adduced of its existence the assumption of such an agent is purely gratuitous.

More recently two forms of central inhibition have come to be recognized, direct and indirect; direct inhibition, which can occur in a two-neuron arc, probably results from direct polarization effects on the soma of ventral horn cells.

VI

THE SPINAL CORD: FLEXION REFLEX

HISTORICAL NOTE

The flexed posture assumed by the injured limb of an animal was probably recognized in remote antiquity. Descartes spoke of it in *De homine* (1662) and the early students of reflex action, such as Hales, Unzer and Marshall Hall, all drew attention to this form of reflex withdrawal. Modern analysis of the reflex, and the broad interpretation of the reaction as a reflex of defense had to await the work of Sherrington first summarized in 1905 in his Silliman Lectures at Yale. For him the abrupt flexion response is a "nociceptive" reaction designed to remove an injured limb from harm's way; it also plays a part in rhythmic walking movements. The electrical accompaniments of the flexor reflex were first studied by Forbes and Gregg in 1915, and with improved myographic methods Sherrington* used the flexor reflex for study of the more precise details of central nervous reactions. By combining electrical and mechanical records Eccles and Sherrington (1930) have employed the flexor reflex to elucidate the problems of synaptic transmission and central inhibition outlined in the last two chapters.

IN order to analyze the flexor reflex in terms of its motor units, it is essential to contrast in a given muscle the flexor reaction to a single volley of afferent impulses with the response of the same muscle to a maximal motor-nerve twitch. The central nervous system operates through activation of all-or-nothing units, and all modern work has indicated that the individual motor unit activated reflexly behaves in exactly the same way as the same unit activated through direct stimulation of its axon. Hence any differences between the response of a flexor muscle to a motor nerve stimulus, and the response of the same muscle to a reflex stimulus must lie in some feature of reflex activation of many units which is not present when these units are synchronously stimulated through the motor nerve.

CHARACTERISTICS OF FLEXION REFLEX

Experimental examination of the reflexes of warm blooded animals requires complete isolation of the muscle under examination from all other muscles in the limb; and it is furthermore desirable to prevent

* These were first described by Dreyer and Sherrington (1918) and in greater detail with Sassa (1921). A much improved isometric torsion-wire myograph developed under Sherrington's guidance was described by Cooper and Eccles (1929, 1930).

extraneous reflex stimulation from nerves other than the one chosen to evoke the reflex. It is therefore a routine in such studies to denervate all muscles in both extremities, except the one whose response is to be recorded, and to denervate all surrounding skin to avoid adventitious sensory reactions. With such a simplified preparation any reflex response can be attributed to the nerve and muscle under examination.

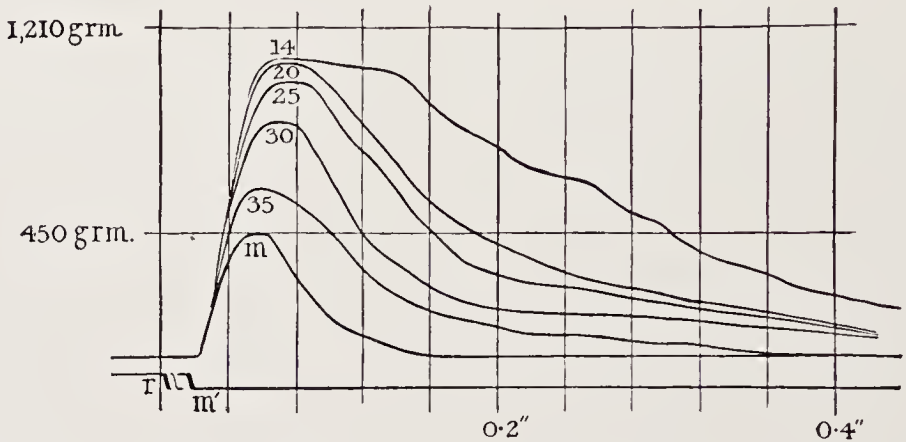


FIG. 29. Tracings of flexor reflex myograms of *tibialis anticus* muscle of spinal cat (all from same experiment) superimposed upon maximal motor nerve twitch of same muscle. Reflexes were obtained by increasingly intense single break-shocks applied to ipsilateral popliteal nerve. Time ordinates marked 25ths of sec. Signal *r* indicates reflex, signal *m'* latency of motor twitch. Thin signal-drop between these gives latency of strongest reflex (Sherrington, *Proc. roy. Soc.*, 1921, 92B, 256).

RESPONSE TO SINGLE AFFERENT VOLLEY. When recorded by an accurate torsion-wire myograph the motor twitch of a decerebrate cat's *tibialis anticus* muscle is similar in shape, but never quite identical with that of a reflex response to a single volley of afferent impulses. The principal differences are as follows: (i) The reflex action always starts less abruptly than the motor nerve reaction, the tension curve being concave upward for an appreciable distance during the ascent, and the point of its inflection occurs at 20 to 30 per cent above the base line (cf. figures of Cooper and Eccles, 1929); the motor nerve twitch may be convex upward from the start. (ii) The maximal tension development may be less in the motor twitch than in the reflex response. (iii) Finally the curve of relaxation of the motor twitch is concave upward, whereas that of the reflex reaction may be convex throughout the greater part of its extent. These differences are accentuated when the intensity of the afferent stimulus is increased, *i.e.*, when more afferent fibres are brought into

action (fig. 29). A series of superimposed tracings of myograms of tibialis anticus muscle of the spinal cat is shown in figure 29, the lowest curve being that of the maximal motor nerve twitch.

From these differences it is inferred: (i) That the impulses from the reflex centre do not arise in a synchronous volley, as in the case of the motor nerve twitch, there being considerable temporal dispersion of the impulses. (ii) The fact that the reflex reaction may be greater than the maximal motor nerve twitch indicates that some motor units discharge repetitively. This is also borne out by the slower curve of relaxation. (iii) The stronger the stimulus the greater the tendency towards repetitive response of motor units. Such repetitive response is referred to as "after-discharge."

RESPONSE TO REPETITIVE AFFERENT VOLLEYS. Further information concerning the behaviour of the reflex centre is obtained through repetitive stimulation: (i) with two or three shocks at varying intervals and (ii) with tetani at varying rates.

Two afferent volleys. When a second stimulus is delivered to an afferent nerve at varying intervals following the first, the response to the second of the two volleys can be inferred by comparing a summated reflex with that induced by the first (the "conditioning" stimulus). The second stimulus is referred to as the "test" stimulus. When the interval between the two centripetal volleys is short, the reflex contraction evoked by the second volley is due largely to the discharge of motoneurons which failed to respond to either volley alone, a point originally established by Forbes (1928) and his co-workers. As Eccles and Sherrington point out (1931b), the response of these additional motoneurons is due to summation of the subthreshold excitatory effects (*c.e.s.*) of each volley. The neurons with elevated *c.e.s.* are said to be in the subliminal fringe of excitation (Denny-Brown and Sherrington, 1928). The least interval at which the second of two successive afferent volleys evokes a response does not therefore serve to measure the refractory period of the reflex arc, since the augmented response comes from motoneurons not previously activated.

By varying the time intervals and intensity of the afferent volleys a period of unresponsiveness of certain motoneurons is readily demonstrated (fig. 28). Eccles and Sherrington (1931b) encountered three types:

1. Recovery complete in less than 16 *sigma*. Here the unresponsiveness is almost certainly a true refractory period following the reflex discharge set up by the first

volley. Its duration is in agreement with the average value of 10.5 *sigma* obtained for the duration of the refractory period of motoneurons following an antidromic volley.

2. Recovery complete in less than 50 *sigma*. In the more prolonged cases the unresponsiveness is due to an inhibition set up by some of the impulses of the first

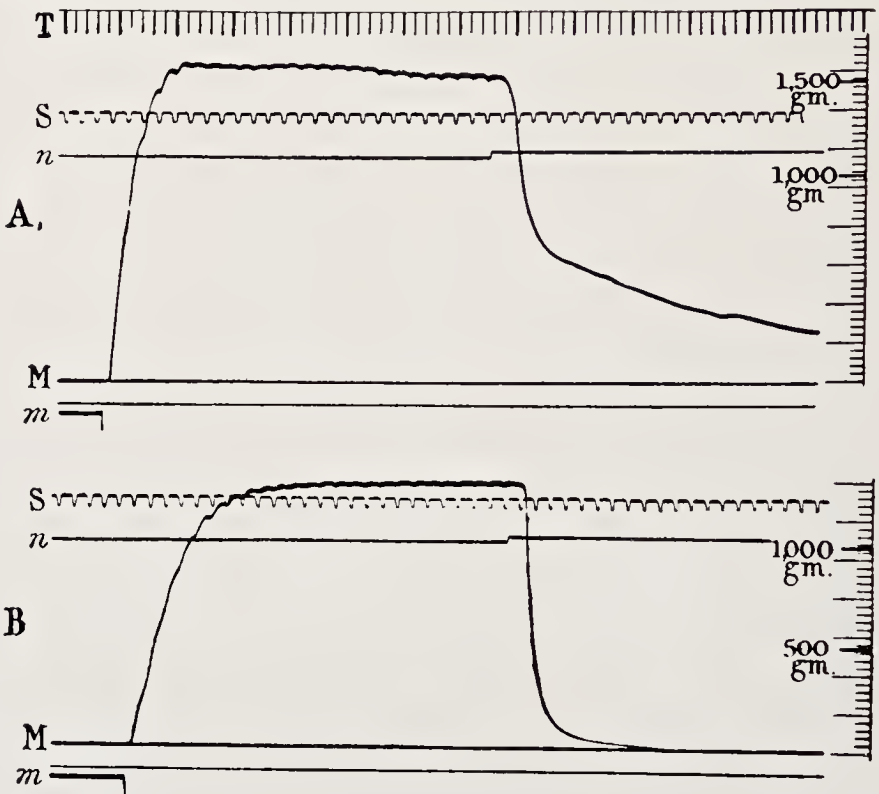


FIG. 30. Tetanic myograms recorded with high frequency torsion-wire lever of *semi-tendinosus* muscle of spinal cat, illustrating differences between reflex tetanus and motor nerve tetanus. Afferent nerve: ipsilateral peroneopopliteal. Time above 0.02 sec. Rate of stimulation 38 break-shocks per sec. Tension record on right. A, Reflex tetanus showing large initial response, poorly sustained plateau and moderate after-discharge. B, motor nerve tetanus of same preparation which yielded reflex response in A (Liddell and Sherrington, *Proc. roy. Soc.*, 1923, 95B, 146).

volley. When recovery is complete in less than 30 *sigma*, it is not known whether the unresponsiveness is due to inhibition or refractory period.

3. Recovery not complete for more than 80 *sigma*. This prolonged unresponsiveness is due to the inhibition produced by some of the impulses in the first volley. This inhibition is similar to the inhibition produced by stimulation of contralateral nerves.

Similar periods of unresponsiveness have been recorded by Gasser (1935) in studying cord potentials: briefer periods of unresponsiveness have also been found in eye muscle preparations by Lorente de N6 (1935f&g).

Afferent tetani. When an afferent nerve of a flexion reflex preparation is stimulated repetitively, the tension curve of the resulting response indicates that the

stimulus rhythm applied to the afferent nerve can be detected in the reflex response at rates up to 40 to 50 per sec. In figure 30 such a reflex tetanus is shown and contrasted with the corresponding motor nerve tetanus of the same muscle (semitendinosus). It will be noticed that the first response of the reflex (A) shows a greater tension value than the first response of the motor nerve tetanus. This is in keeping with the single shock reflex and motor nerve responses just considered. The plateau tension tends to be maintained less well in the reflex than in the motor nerve tetanus, and finally the relaxation of the reflex tetanus is slower. These differences, as in the case of the single reflex and motor nerve responses, can be accounted for by the presence in the reflex response of after-discharge in certain neurons responding to each successive stimulus.

From study of these reflex and motor nerve responses in flexor and crossed extensor reflexes, respectively, Liddell and Sherrington (1923a&b) pointed out that the flexion reflex was *d'emblée*, — all the motor neurons which were to participate in the reflex responded as a result of the first stimulus, *i.e.*, there was no "recruiting" of motoneurons as the stimulus proceeded. This accounts for the abrupt character of the flexion reflex. The crossed extensor reflex, on the other hand, is a "recruitment" type of response (ch. vii).

ANALYSIS OF FLEXOR PATTERNS. Comparisons of direct motor with the reflex responses to the same muscle indicate that no afferent nerve is able to command all of the available motor units passing to a given flexor muscle; some afferents, however, can claim a larger proportion of motor units than others. Small tributary nerve twigs are likely to evoke a larger response than the large parent nerve trunk. This stems from the fact that a large sensory nerve trunk contains fibres of different sensory modalities and hence produces mixed effects upon the spinal centre. In view of the defensive character of the flexor reflex it is likely that stimulation of those fibres which in an intact animal would cause pain are those most potent in the elicitation of the response. This is borne out by the fact that cutaneous twigs evoke a larger response in flexor muscles than do deeper nerves such as obturator. An example is given in the following list of tension values obtained in semitendinosus muscles of a spinal cat. The maximum tension developed in a motor nerve tetanus of this muscle was 3,000 gms. The tensions evoked by the several afferent nerves tested were as follows (Cooper, Denny-Brown and Sherrington, 1926; see also 1927):

	Gm.		Gm.
A dorsal digital	2400	Nerve of sartorius	1500
Another dorsal digital	2550	Nerve of quadriceps, ext. . .	2800
Another dorsal digital	1240	External cutaneous (groin) .	830
Obturator, superficial	1270	Small sciatic	1860
Obturator, deep	630	Anterior tibial	2900
Internal saphenous	1900	Popliteal	2650
Total of both cols.	21,130		

It was also found that the proportion of the total aggregate of neurons supplying a given flexor muscle is smaller in the decerebrate animal than in the spinal, and in the spinal animal is smaller immediately after the spinal cord has been cut than when the effects of spinal "shock" have worn off. The proportion is *increased* by the administration of subconvulsive doses of strychnine.

Final common pathway. A flexor reflex involves simultaneously flexor muscles of hip, knee, ankle and to some extent also the flexors of the digits. Consequently stimulation of an afferent nerve such as dorsal digital evokes contraction simultaneously in the whole flexor group. These muscles which all contribute to the same pattern of response are said to respond "synergically." As indicated in the preceding table, many nerves can evoke the flexor pattern of response. This means that the same motor units are available to a large number of widely separated afferent nerve fibres. This overlap in reflex fields lies at the basis of coordinated action of the nervous system and is generally referred to as the principle of "convergence," many afferent systems converging upon the motor units in the ventral horn. Because of this convergence from many sources, the motor cells of the ventral horn, and the axons to which they give rise, are referred to as "the final common pathway" of the nervous system (Sherrington, 1904). The anatomical basis of convergence lies primarily in the extensive collaterals given off by each sensory fibre as it enters the spinal cord.

Occlusion. When two afferent nerves which produce the flexion reflex are stimulated simultaneously, the tension developed in a given flexor muscle is often very little greater than that evoked by each nerve stimulated independently. Thus when tibialis anticus was thrown into activity by concurrent stimulation of two plantar nerves the tension developed was in one instance 1.8 kg., whereas the two nerves separately gave 1.57 and 1.58 kg., respectively. The deficit of tension is referred to as "occlusion" and is to be explained by the fact that the two plantar nerves activate a certain proportion of the same motoneurons. When both nerves are stimulated simultaneously, a few of the subliminally excited motor units are added to the reflex with the result that a slight increase in tension occurs. For a more detailed discussion of the principle of occlusion see Creed, *et al.* (1932, pp. 25-29).

AFTER-DISCHARGE. The fact that a given afferent stimulus causes motoneurons to discharge more than once, even when the afferent stimulus

consists of a single volley of impulses, has already been mentioned. Actually the discharge from such a volley may continue for a second or more, especially in the extensor group of reflexes. In flexor reflexes after-discharge continues for only 60 or 70 msec. Forbes (1922) postulated that this continuation of discharge is due to internuncial reflex circuits or "delay paths." Since the refractory period of the motoneuron is of the order of 10 to 15 msec. (ch. iv), reverberating internuncial circuits must continue to excite the ventral horn cells throughout several cycles of discharge and recovery. The explanation suggested by Forbes of after-discharge is the only one that has been widely accepted, and it seems unnecessary to discuss alternative hypotheses. With the intact nervous system and the "long circuiting" of sensory impulses to levels of higher integration, the possibility of delayed discharge is almost infinitely multiplied. After-discharge in the simple spinal reflex therefore becomes one of the basic manifestations of nervous function.

CLINICAL IMPLICATIONS OF FLEXION REFLEX

The flexion reflex plays an important part in injury, and in many of the more common diseases. The attitude of the subject undergoes a striking change as a result of nociceptive stimulation in various parts of the body. For purposes of description such changes may conveniently be divided into three main groups depending upon the anatomical location of the irritation. It may arise: (i) within the cranial cavity, (ii) within the abdomen or (iii) in association with one or more of the four extremities.

IRRITATION OF DURA MATER. One of the early symptoms of meningitis is a tendency towards retraction of the head. This is a characteristic sign of stimulation of the pain endings of the fifth cranial nerve, and from cases of meningitis it would appear that the irritation of the dura at *base of brain* and along the tentorium is more effective in causing retraction of the head than stimulation, for example, of the dura over the cerebral hemispheres. However, reflex contraction of the extensor muscles of the neck is not pathognomonic of stimulation of the fifth nerve, for in a decerebrate animal slight degrees of head retraction are seen in response to stimulation of almost any sensory nerve in the body, but it is usually much more pronounced and persistent in response to stimulation of the fifth nerve. It may also be evoked in a decerebrate preparation from pinching or pulling the dura, especially at the base (personal observa-

tions). During operations on man conducted under local anesthesia tension applied to the dura along the line of its attachment to the sella turcica gives rise to intense pain and occasionally to reflex contraction of the neck muscles.

The physiological significance of head retraction is rather less obvious than one might at first believe. Anatomically it is an extensor reflex; physiologically retraction of the head often occurs in association with spasms of extensor rigidity such as one sees in animals after decerebellation. However, when it occurs in response to a painful stimulus it is associated with generalized flexor spasm of the muscles of the extremities, and clinically one of its most conspicuous associated reflexes is a slight flexor contraction of the hamstring muscles, a condition which is referred to in clinical literature as the *sign of Kernig* *(1907). If one attempts in an early stage of meningitis forcefully to extend the knee, the patient complains of pain in the hamstring muscles and on palpation it is evident that this muscle group is in a state of moderate reflex contraction. It is often stated that the sign of Kernig is pathognomonic of meningitis. In the presence of other well marked meningeal symptoms this is probably true, but it should be recalled that it occurs in cases of peritonitis or occasionally in arthritis.

The occurrence of extensor rigidity in association with head retraction in cases of cerebellar lesions is possibly due to chronic irritation, but more likely a manifestation of transient decerebration (Jacksonian cerebellar seizures, 1871). In clinical cases of cerebellar tumour, head retraction is always associated with the more rapidly growing invasive tumours (medulloblastomas) which frequently produce the decerebrate syndrome (Bailey, 1933).

IRRITATION OF ABDOMINAL AND THORACIC VISCERA. Hippocrates was familiar with the "doubled up" attitude assumed by human beings suffering from peritonitis. The posture carries with it an obvious biological purpose since it is clearly a defensive reaction, and it enables the great omentum to cover the abdominal viscera and so to combat and localize infectious processes. Normally in the erect posture of a well developed

* Vladimir Michalovich Kernig (1840-1917), the distinguished Russian neurologist and clinician, had his medical education at Derpt (Esthonia) and from 1865 to 1911 served as Director of the Obuchovsky Hospital in Leningrad. He was largely responsible for making possible medical education of women in Russia. I am indebted to Dr. Nicolay Propoy-Graschenkov for this information. Unfortunately Kernig is little known among English medical writers.

male the omentum covers only the upper part of the viscera. When a patient is in the "doubled up" posture with legs flexed, the omentum covers both the abdominal and the pelvic viscera; the subject moreover is immobilized which is essential for the walling off of the infectious process. In a series of well controlled observations carried out by F. R. Miller (1924) and with Waud (1925a&b) reflexes elicitable from stimulation of individual abdominal viscera were studied in detail. They were carried out chiefly upon decapitated cats.

Stomach. When this viscus was distended with air or was filled with concentrated mustard (or mustard oil), the abdominal muscles began to contract after a period of 4 to 5 minutes and a series of progressive movements were executed by the hind extremities. There appeared to be marked enhancement of reflex activity of the extremities, trifling stimuli evoking vigorous flexor responses. Manipulation of the stomach caused great enhancement of abdominal rigidity and hind limb movement. Section of posterior roots of the 7th, 8th and 9th dorsal segments greatly diminished but did not entirely abolish the effects. Section of the splanchnic nerves also did not completely abolish the response. Extirpation of the coeliac and superior mesenteric ganglia on both sides, which in itself caused powerful responses of the abdominal muscles and hind limbs, was followed by complete cessation of all evidence of stimulation from gastric mucosa. Further details of Miller's work are given in chapter VIII.

Bladder (see ch. VIII). It has long been known that spinal man tends, when his bladder is full, to assume a flexed posture at the hip. Dusser de Barenne and Ward (1937) have studied the urinary bladder reflexes experimentally in cats and monkeys, finding that when the intravesical tension is abruptly increased in a spinal cat the flexor muscles of the hip contract and the knee jerk is reflexly inhibited as in any other flexor reflex (principle of "reciprocal innervation," cf. ch. VII). Similar reactions were obtained from sudden distension of the gall bladder and the intestines.

Peritoneum. The peritoneum was thought at one time to be without sensibility, for it can be cut, burned and at times even stretched in a conscious patient without giving rise to pain. However in the presence of inflammation the peritoneum may be exquisitely painful to touch or to gentle traction. Histologically it is richly supplied with sensory endings of the encapsulated as well as of the more primitive type known to subserve pain in other parts of the body (Sheehan, 1932; ch. 1). These endings are associated with fibres which pass to the spinal cord chiefly by way of the splanchnic nerves. In the cat, and probably also in the human being, the posterior roots subserving these sensory fibres are the 10th, 11th, 12th and 13th dorsal and the 1st post-thoracic segments. Physiological studies upon the response to stimulation of these nerves have thrown light upon the mechanism of the posture which occurs in generalized peritonitis.

One of the outstanding features of a peritoneal infection is the so-called abdominal rigidity. This is brought about by contraction of the rectus abdominis muscles. When the central end of the splanchnic nerve or of the superior mesenteric nerves is stimulated by a faradic current, reflex contraction of these abdominal muscles occurs and persists as long as the stimulation lasts; it also occurs when the lower intercostal nerves supplying the skin of the abdomen are stimulated. The

flexors of the hip also respond, especially to stimulation of the splanchnic nerve. This gives to the animal a posture similar in every detail to the "doubled up" attitude so often seen, *e.g.*, in the case of a ruptured appendix, and there is every reason to believe that the essential reflex mechanism is the same.

There is a close relation between the sensory innervation of the skin and that of the peritoneum immediately beneath it; thus in an early case of appendicitis there may be no abdominal spasm until the skin over the appendix is gently touched. Presumably the combination of persistent slight stimulation of the peritoneum in the affected area becomes summated with the nerve impulses arising as a result of touching the skin in the same region. The observations of Weiss and Davis(1928) on the effect of anesthetizing the skin in cases of extreme abdominal pain strongly support this belief. They have observed, in cases of renal colic, that the most incapacitating attacks of pain are ordinarily promptly relieved by injecting the skin of the abdomen on the same side with novocaine. It is not yet known whether this is due to summation in the centre or to actual dichotomy of individual fibres, some passing through the skin and some to the peritoneum of the same segment.

The physiological significance of abdominal rigidity and the associated posture of the lower limbs is much more obvious than in the case of head retraction, for the posture is one of a generalized flexor reflex affecting the whole abdomen and lower extremities. Stimulation of certain sensory nerves passing to the lower extremities also produces contraction of the abdominal muscles in association with a flexor response of the limb on the side stimulated. The attitude is thus similar to that assumed on painful stimulation of nerves of the lower extremities. The biological significance of the "doubled up" posture concerns not only omentum, but the physical condition of the whole animal. A flexor reflex prevents the subject from standing on his feet and he must therefore stay quiet.

IRRITATION OF EXTREMITIES. In human beings the lower extremities are more simple in their reflex behaviour than are the upper extremities in which the cerebral hemispheres have come to play a dominating role as a result of the assumption of the erect posture. The lower extremities in men behave as do those of animals, and their responses in an intact human being are in many ways similar to those of spinal man. Thus when the bottom of a man's foot is pricked or burned it is reflexly withdrawn whether he is in a spinal state or in normal physiological condi-

tion. Similarly, a dog with a thorn in its hind foot holds up the extremity and runs away on his three other legs. This is the result of a generalized flexor reflex the intimate mechanism of which has been carefully studied in man as well as in animals. When in a resting hind limb a nerve is stimulated or the skin is pinched the flexor muscles contract and the extensor muscles at the same time relax (ch. VIII). This is due to reciprocal innervation of the opposed muscle groups.

Chronic arthritis. The posture assumed in chronic arthritis of the lower extremities is readily understood. The semiflexed position is well known and is the result of persistent painful stimulation arising in the surfaces of the joints. One of the striking features of long standing cases of arthritis, *e.g.*, of the knee, is a wasting of the extensor muscles. This can only be due to persistent inhibition of the extensor muscles resulting from reciprocal innervation. The atrophy is therefore one of disuse. Harding (1929) has published observations upon experimental arthritis in animals and has recorded that marked atrophy occurs in the quadriceps muscle. For some reason not at present well understood flexor muscles of the hip also share the generalized atrophy seen in the extensor group at thigh and ankle, as has been pointed out by Rendall (1928).

Babinski response. Another important illustration of the flexor reflex in man is the so-called "sign of Babinski" (1896, 1898). This is a reaction which occurs after the pyramidal pathway from the cerebral cortex is interrupted. It is mentioned here because the reaction is a typical flexion reflex characterized by upgoing of the great toe and simultaneous contraction of the flexors of hip, knee and ankle. The withdrawal phase of the Babinski response occurs also in the lower animals; thus in monkeys and baboons, after ablation of the foot area, marked withdrawal of the paretic extremity occurs on pinching the skin of the sole, or, for that matter, the skin of any part of the extremity (Fulton and Keller, 1932). In the baboon the reflexogenous zone actually spreads throughout the entire body so that on pinching the ear one may obtain a withdrawal response. But in monkeys the extension of the hallux does not occur unless an entire cerebral hemisphere is removed (Forster and Campbell, 1942); this latter reaction, however, is found in the chimpanzee, where it appears in a form entirely similar to that in the human being after isolated removal of the foot area. The upgoing of the toe is in reality a part of the generalized flexor reflex of the extremity as a whole. The reflex may also be evoked by flexion of one of the outer toes both in man and chimpanzee (Gonda, 1942). In man the withdrawal phase may, with weak stimulation, be slight, or practically non-existent.

SUMMARY

The flexion reflex is the most primitive pattern of response of higher vertebrates, representing the mechanism for withdrawing an extremity from injury. In the language of Sherrington, it is usually a "nociceptive" response—a reaction to a noxious stimulus.

The flexion reflex is conspicuously present in the spinal animal and has been used to study many fundamental properties of transmission in

the central nervous system(ch. iv). It is a segmental spinal reflex generally involving muscles innervated by several segments, *i.e.*, all the flexors of hip, knee and ankle simultaneously; digits may also be involved. Hence, a single afferent nerve has the capacity to command many motor units. Some nerves, however, command a greater proportion of units than others. In general, smaller nerve twigs to the skin excite a larger number of flexor units than the deep sensory nerves.

When two sensory nerves are stimulated concurrently, they may produce little more tension than either one alone("occlusion"). After-discharge is also conspicuous in flexor reflexes and is looked upon as due to continuous discharge among internuncial reflex circuits.

Clinically, flexor reflexes are seen in many forms of chronic irritation. Thus in meningitis, when the coverings of the brain are inflamed, the neck is retracted and there is a flexor response at the hip(Kernig's sign). When the abdominal viscera are irritated, as by a ruptured appendix, the rectus abdominis muscles contract, causing the body to assume a doubled-up attitude. Flexor muscles simultaneously contract and this has the effect of immobilizing the animal and of causing the omentum to slip down over the infected area to wall it off.

In chronic irritation of the extremities, such as that occurring in arthritis of the knee joint, chronic semiflexed postures are seen and, owing to the principle of "reciprocal innervation," the extensor muscles undergo atrophy.

When the bladder or other abdominal viscera are abruptly distended in the spinal animal, the contraction of rectus abdominis and of the hip flexors occurs.

VII

THE SPINAL CORD: EXTENSION REFLEXES

HISTORICAL NOTE

The significance of the flexion reflex as a response to injury was early appreciated, but the meaning of extensor reactions in the economy of the organism has not been as fully understood. The "slight constant tension which is characteristic of the healthy living muscle" was thought to be a property of any muscle having connections with the nervous system. This "tonus" was detected in many muscles irrespective of their anatomical position. Brondgeest(1860)demonstrated that the flexor tonus of the fore- and hindlimbs was diminished after section of appropriate posterior roots, and he attributed the alteration to the abolition of the "tonic reflex of the frog's hindlimbs." The observation was soon confirmed, and Eckhard (1881)extended the concept by intimating that the resting contraction of so-called healthy muscles is not uniform in degree, but had a functional distribution. Mommsen(1885)observed that the Brondgeest experiment still held after the extremity had been stripped of its skin; evidently, therefore, the reaction depended upon sensory nerve fibres from the muscles themselves. In 1898 Sherrington discovered that the phenomenon of decerebrate rigidity(ch. ix)disappeared entirely after severing the dorsal nerve roots. The reflex significance of the tonic extensor reflex did not, however, become obvious until Liddell and Sherrington (1924)described the stretch reflex and Denny-Brown and Liddell(1927)had proved it a reaction integrated at the spinal level(see also Matthes and Ruch, 1933).

THE extension reflexes, which play such an important part in the postural reactions of vertebrates, were first subjected to physiological analysis by Sherrington(1898). His description of decerebrate rigidity indicated that "tonus" was not distributed indiscriminately in the limb musculature of all vertebrates, but occurred most markedly in those muscles which normally counteract the action of gravity, *e.g.*, the extensors. Furthermore, when the forebrain of a cat or of a monkey is removed the animal assumes a posture that simulates reflex standing. Extensor muscles which normally counteract effects of gravity are rigid and the posture becomes "an exaggerated caricature of reflex standing": the limbs are vigorously extended, the jaw tightly closed by the masseters, and the tail extended. In 1915 Sherrington wrote as follows upon the distribution of tonic reactions in extensor muscles:

"... Reflex tonus obtains in, and is confined to, those muscles which maintain the animal in an erect attitude. That this is so may be demonstrated by set-

ting the decerebrate preparation on its feet; it is then seen that the preparation stands. Thus this reflex tonicity, which when seen in a single isolated muscle prepared for the myograph, does not carry on the face of it any very obvious biological purpose, does carry a clear and unmistakable biological purpose when the phenomenon is followed in the musculature as a whole. *The reflex tonus is postural contraction. Decerebrate rigidity is simply reflex standing.* The reflex tonicity of the skeletal muscles of the decerebrate cat and dog is shown by its co-ordination, its effects, and its distribution in the musculature, to be a reflex which differs from the reflexes more commonly studied mainly in this, that the latter execute *movements* while this maintains *posture*."

The exaggerated extensor responses which Sherrington described are now known to be due to the stretch reflex. A short account will therefore be given of this reaction, and the mechanism concerned in its maintenance will then be outlined.

STRETCH REFLEX

Sherrington had long known that the extremities of an animal exhibiting decerebrate rigidity resisted passive movement of its limbs. Careful examination revealed the fact that this resistance is most prominent in the antigravity muscles, of which the knee extensors and masseters are classical examples. This led Liddell and Sherrington (1924, 1925a) to the study of the "myotatic" or stretch reflexes. Using the fully isolated quadriceps muscle of the cat in an extremity in which all other nerves, cutaneous and muscular, had been severed, the only sensory nerves in connection with the nervous system would be those arising in the muscle itself. With the pelvis securely fixed to an experimental table, and the patellar tendon dissected free and attached to a rigid myograph, it was possible by slowly lowering the experimental table to examine the response of the muscle to simple stretch. If the muscle was stimulated in this manner, a relatively enormous tension was developed in response to only a few mm. of passive extension (fig. 31). That this tension was active and not passive was established in the following manner.

Reflex tension and passive tension. If the quadriceps of a decerebrate cat is stretched by 8 mm. in 1 sec., the myograph rises rapidly, then gradually descends as the stretch is continued. The reflex origin of the tension so developed is indicated by the following lines of evidence: (i) If the nerve is cut, the tension is far less, certainly not more than 20 per cent of the reflex tension just described (fig. 31). (ii) The curve developed by a denervated muscle is entirely different in contour from that of an active muscle. (iii) When the dorsal nerve roots are severed, the

muscle on stretching behaves as though its nerve were cut.(iv) Much more convincing evidence of the reflex origin of the stretch reflex is the fact that it can be inhibited along with other extensor reflexes by stimulation of any homolateral sensory nerve of the hindlimbs(fig. 32). Such an inhibitory stimulus, if of adequate strength, may bring the myograph completely down to the level of the new base line imposed by the

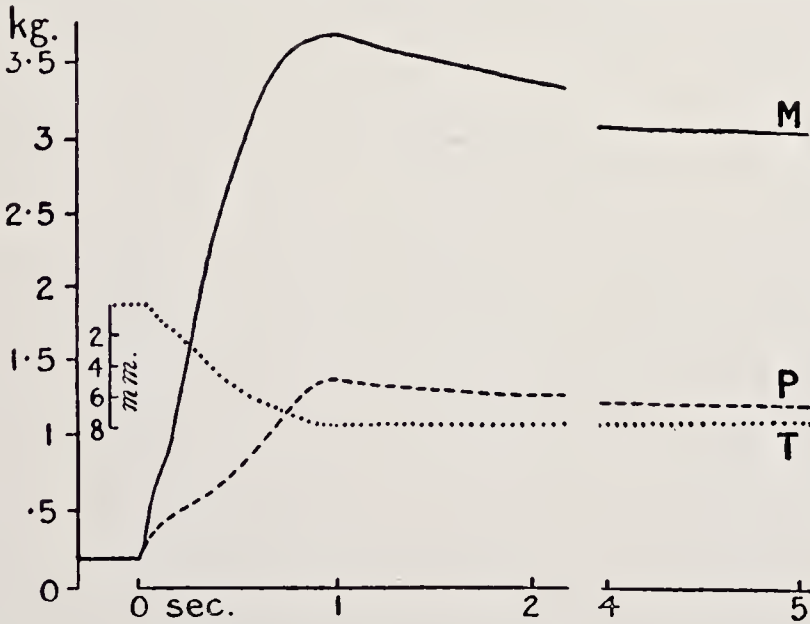


FIG. 31. Stretch reflex of quadriceps muscle of decerebrate cat. Tension is indicated on left, dotted line designates extent of fall of table in mm. Smooth curve M indicates muscular response to stretch of 8 mm. before severing nerve. Broken line P, same response after nerve had been severed. Time indicated in sec. (Liddell and Sherrington, *Proc. roy. Soc.*, 1924, 96B, p. 213).

passive elongation of the muscle. If the inhibition occurs before the stretch is applied, the muscle describes a curve similar to that of a muscle whose motor nerve has been severed(fig. 32). On these grounds, it is permissible to conclude that the reaction of the quadriceps muscle to stretch is an active reflex contraction.

Characteristics of stretch reflex. The characteristics of the stretch reflex have been described elsewhere(Fulton, 1926, pp. 364-382). It arises in the first place from the muscle itself, since, when all nerves to the hindlimbs except those to quadriceps are severed, the stretch reflex remains. Severance of the posterior nerve roots destroys it, but local anes-

thetia of the tendon itself has no effect upon the reaction. It is quite clear, therefore, that the reflex results from stretch of the muscle itself.

It is generally stated that the myotatic reflex consists of two phases: (i) a phasic reaction corresponding with the period of increasing stretch, and (ii) a postural reaction corresponding with the period during which the stretch is maintained (fig. 31). In other words, the slowness of adaptation of the stretch afferents (ch. 1) allows continued discharge to the cen-

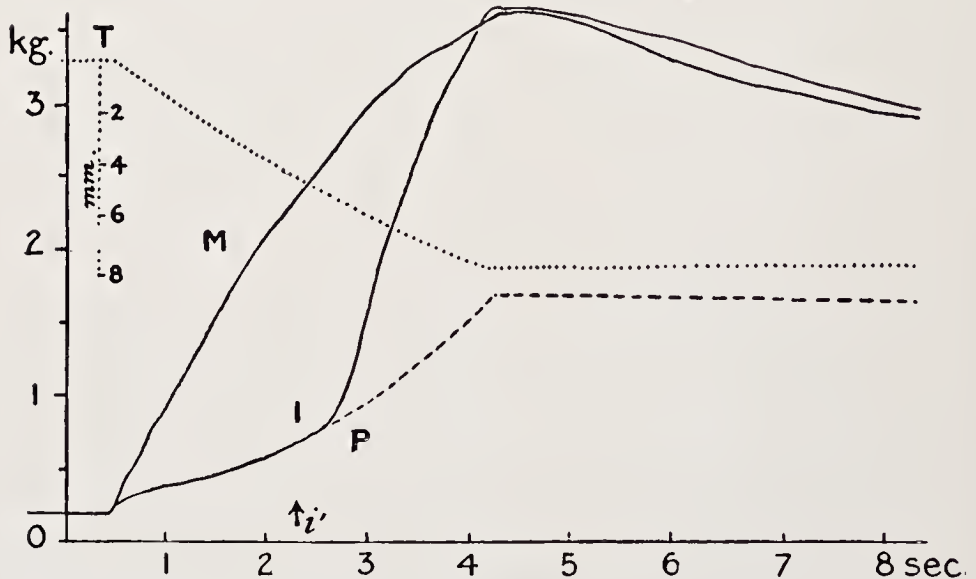


FIG. 32. Vastocurreus muscle of decerebrate cat showing effects of inhibition on stretch reflex. Reaction of uninhibited muscle M is shown in first curve. In second, inhibitory afferent nerve was stimulated before reaction started and was discontinued at i' ; thereafter tension rose to height of uninhibited muscle. Fall of table T indicated by dotted line (Liddell and Sherrington, *Proc. roy. Soc.*, 1924, 96B, p. 232).

tre during the phase of unaltered application of tension. The muscle may be left under stretch for a long period of time and the reflex character of the response can easily be demonstrated by applying a stimulus to an ipsilateral nerve. Such reactions may continue for a period of 30 minutes or more without apparent fatigue. There tends in the early period of the postural phase of the stretch reflex to be a gradual diminution of tension, but this failure is scarcely detectable after several minutes. The postural phase of the stretch reflex is more susceptible to disturbances by spinal lesions, etc., than the phasic period (Denny-Brown and Liddell, 1927a).

In general, the stretch reflex is restricted to the muscle stretched. How-

ever, in a highly sensitive preparation, when a single digit is extended, the other digits may respond to some extent in synergic contraction. Another feature of the stretch reflex is the absence of after-discharge: *i.e.*, once the stretch ceases, the tension immediately subsides to the base line without an appreciable period of after-contraction such as occurs with most other extensor reflexes. It is, however, safe to conclude that the after-discharge is not greater than 1 to 2 repetitive volleys. Though the tension remains constant under conditions of unaltered stretch, there undoubtedly occurs a successive "recruitment" of additional motor units during the period that stretch is increasing. Liddell and Sherrington(1924, p. 220) have described this phase of the stretch reflex as follows:

"The build of the quadriceps, especially of its vastocruureus portion, suggests that as the pull of the patellar tendon on the muscle increases, namely as the stretch increases, the mechanical stretch involves progressively increasing numbers of the muscle-bands composing the muscle. The increase of the reflex contraction as the stretch proceeds would therefore be explicable by corresponding increase of the number of receptors in the muscle coming under the influence of the mechanical stimulus. This is supported by several features of the reflex contraction. Thus, the increase of contraction goes on fairly equably so long as the stretch continues being equably increased, and all irregularities in the process of the stretch are closely reflected in the contraction ascent. . . . One thing that the ascent portion of the reflex contraction shows is the extreme delicacy of the grading of the contraction in accordance with grading of amplitude of the passive stretch imposed. Increase of the stretch is accompanied by increase in the number of its proprioceptors stimulated and of the motoneurons excited which supply it."

The latency of the stretch reflex is a matter of a few msec. Thus Liddell and Sherrington concluded it could not be more than 20 msec. and Fulton and Liddell(1925b), in studying the electrical responses of the stretch reflex, found that the reaction occurred within 6 to 9 msec.

Functional significance of stretch reflex. Sustained stretch reflexes have been observed, not only in decerebrate preparations, but at other functional levels: in decorticate preparations and in chronic spinal animals(Matthes and Ruch, 1933). In the latter, the phasic period of the reaction is erratic and unpredictable. However, the reaction is so ubiquitous among the antigravity muscles that it clearly has functional significance. "Elicitation by gravity of the stretch reflex of the limb extensor suggests itself as a basic factor in this static geotropic reflex of standing. As such it offers an explanation of the postural contraction counteracting gravity, of the proprioceptive nature of that reaction, and

of the latitude of detail allowed to the standing posture of the limb" (Sherrington, 1924b).

The relation of the stretch reflex to the positive supporting reaction described by Magnus (1924) deserves mention (ch. x). The positive supporting reaction is evoked by contact with the pads of the foot, either

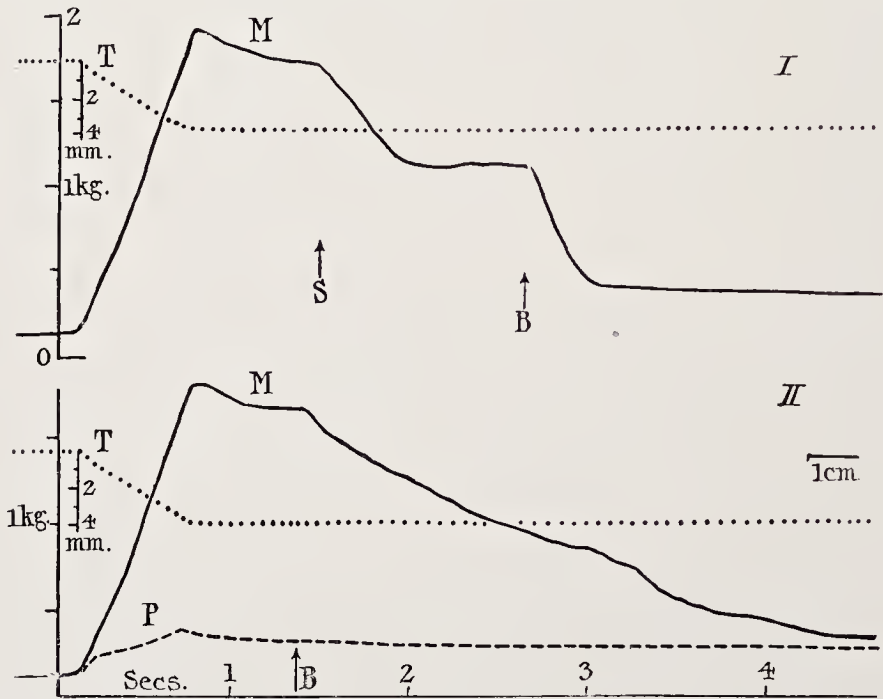


FIG. 33. Response of quadriceps to stretch of 4 mm. before (M) and after (P) severance of its nerve. During response in each record opposing semitendinosus muscle was stretched at arrow S. At arrow B biceps muscle was stretched. Both caused marked inhibition of reflex. In lower curve (II) biceps was stretched slowly (Liddell and Sherrington, *Proc. roy. Soc.*, 1925, 97B, p. 276).

fore or hind, in decerebrate animals. The reaction is obtainable after the skin has been anesthetized; the most potent stimulus appears to be the slight separation and stretch of the interosseus muscles occurring when the foot pads are brought into contact with a solid surface. The reaction appears to augment the stretch reflex and in itself is essentially a myotatic reaction. The stretch reflex can interact with any other form of reflex contraction such as a crossed extensor reflex.

Effects of flexors. Further evidence of the reflex origin of the stretch reflex comes from the fact that stretching an opposing flexor muscle serves dramatically to inhibit any existing reaction in the extensor (Lid-

dell and Sherrington, 1924), especially its stretch reactions (fig. 33). This assumes special importance in relation to the reflex mechanism of stepping (ch. viii).

RED AND WHITE MUSCLES

It has long been recognized that sustained contractions are maintained with surprisingly little expenditure of energy. In lower forms like the bivalve mollusc special muscular mechanisms exist which allow "fixation" of adductor muscles at a given length. The question has, therefore, been raised whether in higher animals corresponding mechanisms exist to facilitate long-sustained postural reactions such as those essential for reflex standing, etc. Some have suggested that the autonomic nervous system is essential to sustained contraction, thus forming a part of a postulated fixing mechanism. All recent evidence (Fulton, 1926, ch. xvi), however, opposes such a possibility, for complete ablation of the sympathetic division of the nervous system destroys no one of the postural reactions, such slight alterations as occur being attributable to secondary vasomotor disturbances (Phillips, 1932) and the associated change of threshold of sensory end organs in muscle. Thanks to the work of Magnus (1924), Rademaker (1931) and others, many specific postural reflexes are now well known, and it has been firmly established that they all depend upon the integrity of the somatic division of the nervous system.

If postural reactions as well as quicker phasic movements thus depend upon the somatic system, does this division of the nervous system make any distinction between a phasic and a postural reaction? Study of the peripheral effectors involved in the stretch reflex indicates that it does, for in all muscles in which stretch reflexes can be obtained there exist two distinct types of muscle fibre: one which tends to be red, due to muscle hemoglobin, and another which tends to be white in colour. Ranvier (1874a&b) and Grützner (1887) early demonstrated that the motor nerve twitch of a red fibred muscle was several times more prolonged than that of the white fibred muscle of the same animal (fig. 34). They suggested that red fibres were called into action when slow movements were required. Hay (1901) showed that the red fibred soleus muscle of the rabbit was innervated by somatic fibres of the ventral nerve root, but that the motor fibres were somewhat smaller in diameter than those passing to the white fibred muscles of the same limb (sensory fibres are about equal in size). Data concerning the distribution of red muscles in

man and other animals was collected by Denny-Brown(1929b). He points out that the pectoral muscles of soaring birds, and especially of migratory birds, are made up largely of red fibred muscle, whereas the pectoral muscles of chickens, turkeys and others not accustomed to sustained flight are made up principally of white fibres. In man and higher vertebrates the distribution within the body is also significant. Every extensor muscle has a deep red fibred head. Thus in the quadriceps muscle, vastus internus is principally red, whereas vastus externus is primarily white. Similarly in the gastrocnemius-soleus complex the inner muscle mass(soleus)is red and gastrocnemius itself white. In most muscles, however, fibres are mixed and in nearly all muscles of the human body some red fibres can be detected. Denny-Brown in a detailed histological study of the problem finds that redness is not necessarily a criterion of slowness, but that the so-called "red" fibres are to be distinguished from so-called white fibres by the presence of large amounts of stored granules(fat).

To Denny-Brown(1929a)is due the credit of having first recognized the significance of red fibres in postural reactions. In studying the soleus muscle of the cat(which is always a "slow" muscle irrespective of how "red" it is)he found that exquisitely active stretch reflexes were present, which suggested to him that red fibred muscles, rather than white, were primarily active in these postural reactions. In turning to a muscle such as quadriceps, he found that the red fibres were indeed the "low threshold units" for the stretch reflex, but that with extreme degrees of stretch the white fibres might also participate. In a given reflex response he was able to determine whether white or red fibres were responding by the *duration of reflex contraction following the application of an inhibitory stimulus*. Since the twitch contraction of red fibred muscles is longer than that of white, it is impossible for an inhibitory stimulus to abolish contraction as early in a red fibred reflex as in a white; as the difference in twitch duration may amount to 300 to 400 per cent(fig. 34), the presence of an extensive red fibred component in a given reflex contraction can be easily recognized. In the case of quadriceps, a crossed extensor contraction which employs white fibred units could be inhibited within about 50 msec., whereas with the stretch reflex of quadriceps an interval of 140 to 150 msec. was required. The electrical responses, however, were abolished simultaneously, so the differences must have been due to the activity of different groups of peripheral fibres.

Further evidence of the participation of red fibres in the postural reactions came from an analysis of the reactions of a white and a red fibred muscle attached to separate myographs in response to the neck and labyrinthine reflexes. As indicated in figure 35, rotating of the chin towards the recording muscle, which gives rise to increased extensor contraction (ch. x), causes only the red fibred muscle to give an appreciable response. From this body of evidence we may conclude that red fibred muscles are the peripheral effectors of sustained contraction.

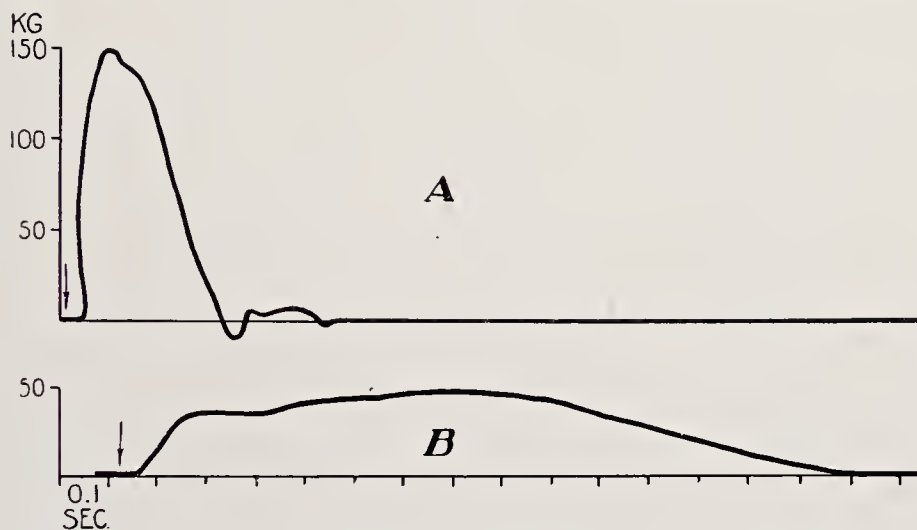


FIG. 34. Twitch contractions of white and red muscle compared. From rabbit's semi-membranosus (upper curve) and soleus (lower curve). Note conspicuous differences in duration. Time indicated in 0.01 sec. (Hay, *Lpool med.-chir. J.*, 1901, 41, p. 433).

Denny-Brown has succeeded in recording the response of single motor units of soleus muscle to a stretch stimulus. As indicated in chapter III, he found that the rate of response was surprisingly slow (from 5 to 8 per sec., which, however, gives a fused tetanus) and that single units could go on discharging at this rate indefinitely. This disclosure accounts for the extraordinary resistance of the stretch reflex to fatigue and also for the fact that postural responses can be maintained for a long period with only slight expenditure of energy. H. E. Hoff (1933) several years later isolated the response of a single unit of soleus and demonstrated the effect on it of the neck and labyrinthine reflexes. He found that rotating the chin towards the muscle increased the rate of discharge of a single unit, and that rotation in the opposite direction diminished it.

One further point of functional significance is that all physiological

flexor muscles are made up of pale rapid fibres — red fibres being found only among the (single-joint) physiological extensors.

STRETCH REFLEXES IN FLEXORS. In dog and cat sustained contraction is not seen on stretching a flexor muscle. Indeed, the primary effect of stretching a flexor is to inhibit any existing contraction in an extensor. However, a brief tug at a flexor tendon may evoke a short-lived reflex response generally referred to as the "pluck reflex." Thus Asayama (1916) found that the tibialis anticus muscle of the decerebrate or spinal



FIG. 35. Effects of neck and labyrinthine reflexes on red and pale muscles respectively on decerebrate preparations. Thick curve lateral head of triceps (white); lower (thin line) curve medial head (red muscle) (Denny-Brown, *Proc. roy. Soc.*, 1929, 104B, p. 280).

cat gave a distinct tendon jerk, although the tendon itself was not essential for the reaction. The reflex disappeared on severance of appropriate posterior roots. Occasionally short clonic responses are obtained, but never a prolonged contraction. Cooper and Creed (1927b) have reported tendon jerks in the sartorius muscle of a spinal cat. As with the pluck reflex, it is possible that these are nociceptive reactions such as one would expect from stimulating a pain fibre. The flexor rigidity of Dusser de Barenne and Koskoff (1934) does not arise from stretch of the muscles involved in the reflex pattern.

OTHER EXTENSOR REFLEXES

EXTENSOR THRUST. The stretch reflex is a sharply localized ipsilateral response, *i.e.*, it is restricted to the muscle stretched, occasionally spreading to a few closely adjacent synergic muscles. The extensor thrust is also an ipsilateral reflex, but is less restricted, *i.e.*, it is a pattern of extensor response affecting all of the extensor muscles of the limbs. The effec-

tive stimulus is sudden pressure applied to the pads of the foot, or quick separation of the toe pads. It consists of a brief extensor reaction best seen in the hind limbs, although corresponding responses have been recorded by Denny-Brown and Liddell(1927b, 1928)and by Miller(1931, 1934)in the forelimb. The extensor thrust is a fractional manifestation of the positive supporting reaction of Magnus(ch. x), and it stands in the same relation to the positive supporting reaction as does the knee jerk to the stretch reflex. The reflex is primarily proprioceptive in origin, *i.e.*, the end organs reside principally in the small muscles of the foot, but, as with the positive supporting reaction, the touch endings in the skin undoubtedly have an adjuvant effect. A nocuous stimulus to the same area of skin would evoke a flexion reflex. The extensor thrust was first described by Sherrington in the spinal dog; he pointed out that it underlies the mechanism of the gallop.

CROSSED EXTENSION REFLEXES. Crossed extension reflexes are not conspicuous in acute spinal animals, though they may be obtained from single shock stimuli(Matthes and Ruch, 1933)immediately after the cord is cut, lapsing thereafter for several days until the signs of spinal shock (ch. viii)wear off. But they obviously form part of the spinal reflex pattern, since they are conspicuously present in chronic spinal animals. The general features of the crossed extensor reflex in a chronic spinal or decerebrate cat are as follows:(i)It has a long latency of 40 to 100 msec. in contrast to 8 to 10 msec., the latency of the flexor reflex.(ii)The stimulus frequency may not be seen in the reflex, even when the rate of stimulation is as low as 3 or 4 per sec.(iii)The duration of ascent is often many times greater than that of the flexion reflex.(iv)The form of the ascent also differs conspicuously from the flexion reflex, being commonly sigmoid, *i.e.*, commencing gradually in an initial concavity, and thus having a high point of inflexion before attaining its convex portion. In other preparations the response may begin abruptly and then ascend more gradually. These differences must be attributed to the central pathways involved in the reflex, since the motor nerve response of an extensor muscle is in all respects similar to that of a flexor(Liddell and Sherrington, 1923a&b). In figure 36 is shown a weak crossed extension reflex contrasted with the motor nerve response of the same muscle.

The primary difference then between a crossed extension response and a flexion response is in the quality of "recruitment." Successive neurons are called into activity by mere continuation of an unaltered stimulus,

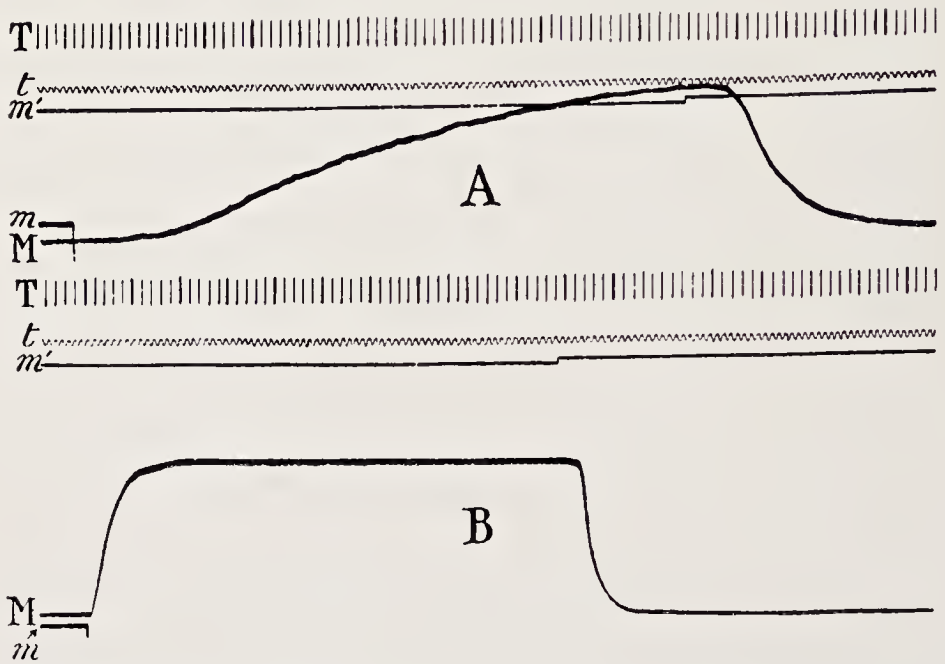


FIG. 36. Crossed extensor reflex of quadriceps compared with motor nerve response of same muscle. A, reflex contralateral peroneopopliteal nerve stimulation at 18 per sec. B, a maximal motor nerve tetanus of same muscle (Liddell and Sherrington, *Proc. roy. Soc.*, 1923, 95B, p. 321).

whereas in the flexor reflex all available neurons are activated at once (ch. vi). Details concerning the influence of posterior root section on the crossed extensor reflex will be given in chapter ix.

RECIPROCAL INNERVATION

It was obvious to the earlier students of the nervous system that coordinated movement involved simultaneous adjustment of opposed muscle groups. Descartes, for example (1662), pointed out that when the external rectus muscle of the eye contracts to produce lateral rotation the internal rectus muscle simultaneously relaxes. Others, however, had suggested that the antagonistic muscle merely remained dormant during the contraction of the protagonist; still others suggested that some degree of contraction was always present in opposed muscle groups to give steadiness to the movement. The concept of reciprocal innervation thus has a long history (reviewed in detail by Tilney and Pike, 1925) which culminated in a series of fourteen papers on the reciprocal innervation of antagonistic muscles published by Sherrington between 1893 and 1909.

In the case of the limb muscles Sherrington finds that the pattern of reciprocal innervation is laid down in the spinal cord(1893). When an ipsilateral flexion reflex occurs in the hindlimbs, the extensor muscles of those limbs simultaneously relax through the operation of the central inhibitory process. He is careful to point out, however, that relaxation

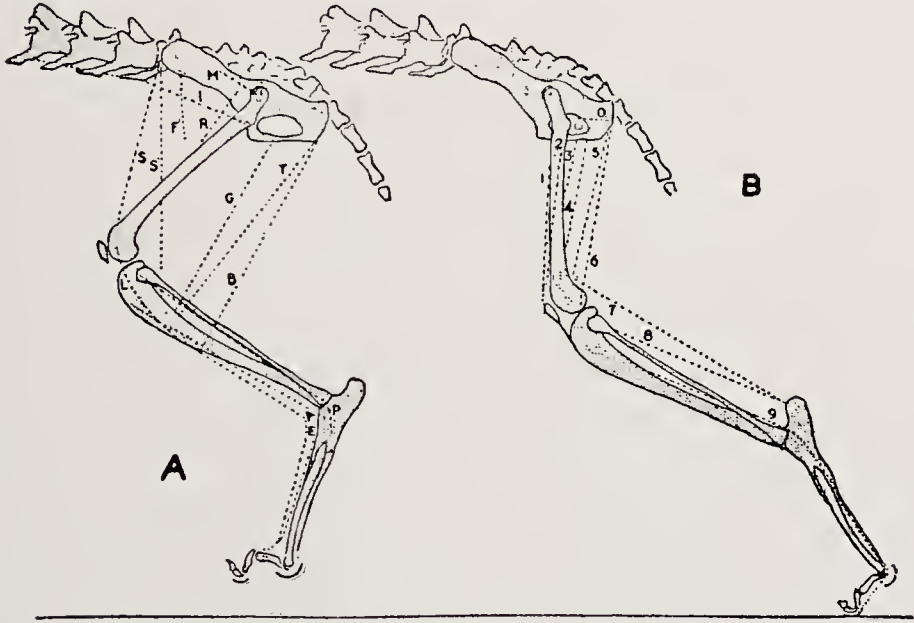


FIG. 37. Diagram illustrating muscles actually observed by experimental analysis to be engaged in contracting in flexion-phase(A) and in extension phase(B) of reflex step of cat. Those which contract in flexion phase are relaxed by inhibition in extension-phase, and conversely. **A.** A, tibialis anticus; B, biceps femoris posterior; E, extensor brevis digitorum; F, tensor fasciae femoris; G, gracilis; I, psoas; L, extensor longus digitorum; M, gluteus minimus; P, peroneus longus; R, rectus femoris; S, sartorius lateralis; S', sartorius medialis; T, semitendinosus. **B.** O, quadratus femoris; 1, crureus; 2, vasti; 3, adductor minor; 4, adductor major(a part); 5, semimembranosus; 6, biceps femoris anterior; 7, gastrocnemius; 8, soleus; 9, flexor longus digitorum. (Sherrington, *Quart. J. exp. Physiol.*, 1913, 6, p. 260.)

of the extensor in these circumstances may not be complete, but proceeds *pari passu* with the development of the flexor response. The principle of reciprocal innervation may then be stated as follows: *Augmentation of contraction never proceeds concurrently in antagonistic muscles and similarly diminution of contraction in antagonists does not occur concomitantly.*

Sherrington's diagram of the muscles involved in reciprocal innervation of the hind limbs is given in figure 37. Those contracting in the flexion phase are indicated in figure 37A; those relaxing in that phase and participating in the extensor phase of a stepping movement are

indicated in figure 37B. Similar reciprocal relations have been demonstrated in the forelimb (Denny-Brown and Liddell, 1927b and 1928; Miller, 1934) and in the eye muscles (Sherrington, 1897). In such co-ordinated reactions as the scratch reflex, which are obtainable in the spinal animal, the principle of reciprocal innervation has also been demonstrated (Brown, 1911). Further examples will be mentioned in connection with the discussion of the postural reflexes in chapter x.

The principle of reciprocal innervation is evident in reactions emanating from the highest levels of the nervous system. It is true that by volitional effort one may cause simultaneous co-contraction of antagonistic muscles (Beever, 1904), but this again in a complex response may be essential for the fixation of a joint and thus have a functional basis, *i.e.*, it does not militate against the principle of reciprocal innervation. We may therefore take it that reciprocal action of antagonistic muscles is a part of the spinal reflex pattern subject to adjustment and modification from the higher levels of the nervous system.

Neural mechanism of reciprocal innervation. The central inhibitory process is clearly at the basis of the central mechanism of reciprocal innervation. The same sensory neuron, on reaching the spinal cord, is able to evoke activity of flexor motor units and at the same time to impair the action of extensor motor units. It is generally assumed that the bifurcating dorsal root fibre innervates, through dichotomy, various groups of central neurons, some of which are internuncial, others of the final common pathway, and that the ultimate motor reaction is appropriate to the particular sensory fibre stimulated. If it is a pain receptor, the primary excitatory connection will be with the flexor units, and the inhibitory connection with internuncials involved in the extensor reflex arc. Gasser's concept (1937) of a positive after-potential and the period of diminished excitability, meets many of the requirements which study of the phenomena of reciprocal innervation have unfolded and would thus appear to be generally applicable (cf. chapter v). The earlier theories of reciprocal innervation have been discussed elsewhere (Fulton, 1926).

SUMMARY

The extensor reflexes, unlike the flexor, are primarily concerned in resisting the action of gravity. They are thus the basic postural reflexes of the body, for in the upright posture gravity tends to cause flexion of

joints such as ankle, knee and hip, and the extensor muscles resist this flexion by active contraction. The resistance develops through operation of a specific reflex known as the myotatic or stretch reflex. The receptors of the stretch reflex are proprioceptors lying in the fleshy region of the muscle itself and the balance of evidence indicates that the muscle spindles are the active endings.

Stretch reflexes have a brief latency (*e.g.*, the knee jerk, 6 to 9 msec.), no after-discharge, and, other things being equal, the reflex continues to increase through recruitment of additional units as the stretch stimulus is increased. During periods of constant stretch, the active tension continues without change and also without fatigue for prolonged periods, *e.g.*, two to three hours.

Evidence of the reflex character of the stretch reflex comes through study of its inhibition and from the fact that dorsal root section or anterior root section completely destroys the reaction.

The central nervous system makes a distinction between the motor units employed for sustained postural reactions and quick phasic movements. For the stretch reflex it uses slowly contracting red muscle units which are generally found in large numbers in the inner head of extensor muscle groups. The rate of discharge of the red muscle motor unit is slow, *i.e.*, 5 to 10 per sec.; moreover, they can maintain this discharge rate for long periods without fatigue.

Stretch reflexes with a sustained postural phase have never been recorded in a physiological flexor muscle, though brief pluck reactions can sometimes be obtained.

When an extensor muscle contracts, its opposing flexor muscle relaxes. This is the principle of reciprocal innervation which is a basic pattern of the spinal reflexes, subject, however, to modification from higher levels of integration.

The two-neuron-arc-reflex discharge results from stimulation of the large, low-threshold afferent fibres of muscle origin (Lloyd, 1943a). This discharge reflects only into the muscle, the head of a muscle or group of muscles the afferent fibres of which are stimulated (Lloyd, 1943c). It has, therefore, the characteristic and restricted distribution of the stretch reflex. In contrast the minimum pathway for the flexor reflex is one of three neurons (Lloyd, 1943d). It appears, therefore, that the two-neuron-reflex paths are reserved for the mediation of the stretch reflex. This view has been confirmed by the demonstration that the afferent response to brief stretch is conducted at an average maximum velocity of 116 M. per sec. and that the stretch-evoked reflex is transmitted through arcs of the two neurons (Lloyd, 1943c).

VIII

THE SPINAL CORD: INTERSEGMENTAL REFLEXES. SPINAL MAN

HISTORICAL NOTE

The earliest students of nervous function recognized that decapitated animals, especially insects (Boyle, 1663, ii, p. 16) and cold-blooded vertebrates, exhibited reflex responses, often complex in nature. As mentioned in an earlier chapter, Marshall Hall (1833) insisted that the isolated spinal cord is to be regarded as essentially a chain of interconnected ganglia made up of segmental reflex arcs. One segment, therefore, must be capable of influencing other segments and the problem of the spinal animal is essentially a problem of the interaction between the spinal segments. Hall was aware that intersegmental reflexes are more readily demonstrated in lower animals than in the higher members of the evolutionary series; he also drew attention to the fact that in higher animals decapitation causes immediate suppression of spinal reactions lasting for minutes or hours. He designates this reflex depression as "spinal shock." Thus in his *New memoir on the nervous system* (1843, p. 30) he says, "Immediately after decapitation, or the sudden amputation of a limb, a diminished condition of the reflex excitomotor power is observed. I divided the spinal cord in a frog; the reflex actions ceased; in a few minutes they reappeared and in a short time they were perfectly restored." A similar description is found in his *Synopsis of the diastaltic nervous system* (1850). The term "spinal shock" has persisted in neurological literature and, though useful, it should be carefully distinguished from so-called "surgical shock." Spinal shock may be defined as "the state of depression of spinal reflexes (hyporeflexia), generally transient in character, which occurs after spinal transection in the bodily segments caudal to the lesion" (Fulton and McCouch, 1937). The various theories of spinal shock have recently been reviewed in their historical aspect by Liddell (1934). More recent concepts will be referred to below.

The phenomena of spinal shock indicate that the segmental nervous system is normally under the influence of the suprasegmental parts of the brain; but the headward segments and the suprasegmental levels are also to some extent regulated by the more caudal segments. As early as 1858, Schiff observed in normal and decerebrate frogs that considerable increase occurred in the irritability of the *forelimb* reflexes after severing the spinal cord below the brachial enlargement. The hyperreflexia so induced could not be due to irritation, since it was present many months after the operation. This cephalad release of function was subsequently observed by Sherrington (1898a) and is hence called the "Schiff-Sherrington phenomenon." Ruch and Watts (1934) and Ruch (1936) found that the Schiff-Sherrington phenomenon is present after all posterior nerve roots caudal to the level of intended transection have been cut previous to severing the cord.

STUDY of spinal animals is essential to an understanding of the nervous system, since the spinal cord mediates the basic reflex patterns upon

which the high centres of the nervous system operate: thus from the isolated spinal cord one may obtain the flexion reflex(ch. vi) and a variety of extension reflexes(ch. vii, crossed extension, stretch reflex and extensor thrust); all these reactions, moreover, follow the principle of reciprocal innervation of antagonistic muscles. These then are purely spinal phenomena — segmental reactions — since they can be demonstrated in short segments of the spinal cord which have been isolated by double transection and by appropriate root section(Sherrington, 1900b, pp. 811–817; see Tower, 1937). In the previous chapters the individual reflexes just mentioned have been described as individual entities. In the present chapter consideration will be given to the manner in which the spinal cord combines and adjusts these reflexes into more complex and purposive movement patterns(somatic and visceral); spinal man and the phenomena of spinal shock will also be given separate consideration.

SOMATIC REACTIONS

Reflex reactions involving the skeletal musculature, as opposed to visceral organs, are referred to as “somatic” since they involve structures developed primarily from the somatopleure. The motor units have their origin in the ventral horns of the spinal cord and since these neurons are played upon by every type of afferent fibre, except possibly those peculiar to the autonomic system, as well as by neurons arising in the suprasegmental levels of the nervous system, and since furthermore these units form the sole pathway from the central nervous system to the skeletal muscles, they are collectively referred to as the *final common path*. That each motor neuron is thus in receipt of impulses from a large variety of afferent neurons follows also on statistical grounds, since the afferent neurons of the body considerably outnumber the somatic motor units.

In *The integrative action of the nervous system*, Sherrington(1906a) pointed out that reflexes which share the final common path leading to a single group of muscles may cause several types of response as follows:(i)sustained contractions such as the flexor reflex,(ii)rhythmic reactions such as the scratch reflex, or(iii)reflex inhibition. The afferent end organs which combine to produce *any one* of these responses are said to be “allied,” and the reactions produced are spoken of as “allied reflexes” because they affect the final common pathway in the same manner. Reflexes, on the other hand, belonging to the separate categories

and therefore opposed one to the other, are spoken of as "antagonistic reflexes." Since the end organs of the body are constantly affected by diverse environmental changes, reflex integration involves the appropriate adjustment of allied and antagonistic reflexes.

ALLIED REFLEXES. There are many examples of allied reflexes: One group already mentioned in the previous chapter is the "positive supporting reaction" and the "stretch reflex," which combine to confer an extensor posture on the limb sufficient to support the weight of the

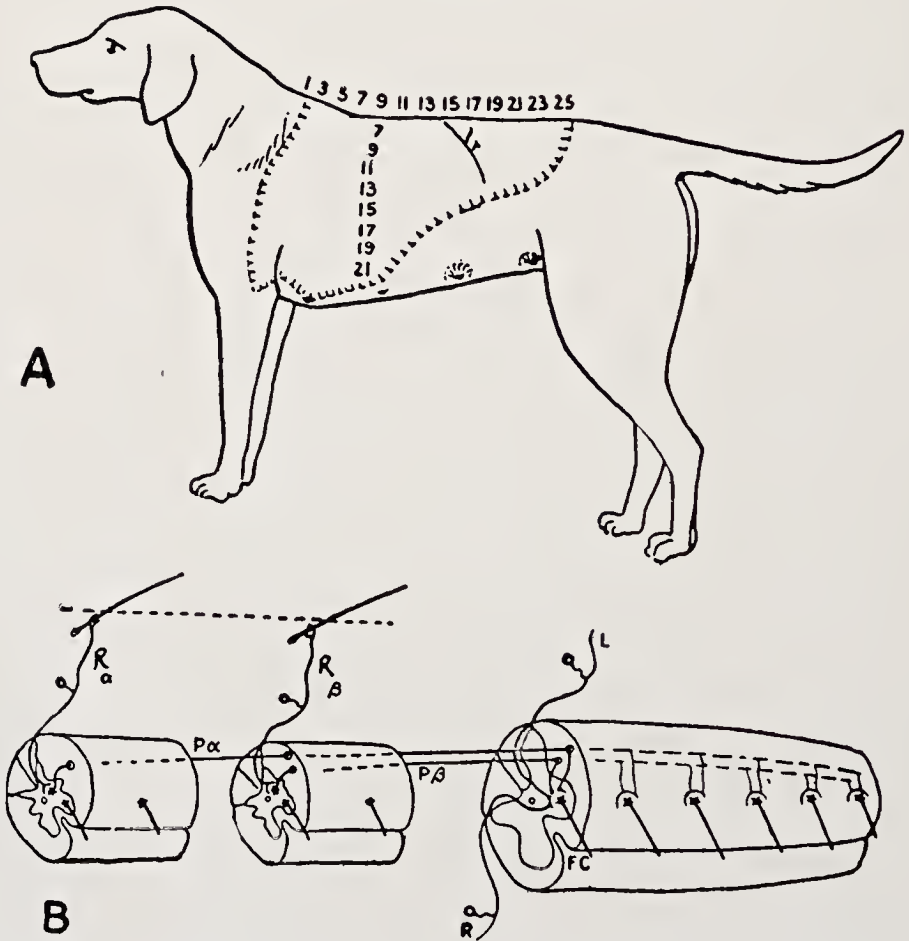


FIG. 38. A, Receptive zone of scratch reflex of spinal dog (low cervical transection). From saddle-shaped area of dorsal skin the scratch reflex may be readily evoked. *lr* marks the position of the last rib. B, Diagram of spinal arcs involved. *L*, receptive or afferent nerve path from left foot; *R*, receptive nerve path from opposite foot; R_α , R_β , receptive nerve paths from hairs in dorsal skin of left side; *FC*, final common path, in this case the motor neuron to a flexor muscle of the hip; P_α , P_β , propriospinal neurons (from Sherrington, *Integrative action of the nervous system*, 1906).

animal against the action of gravity. These synergic reactions clearly fall into Sherrington's first category of reflexes mentioned above. Another quite different type is the "scratch reflex," which would fall into Sherrington's (1906b) second category. These illustrate the principles of simultaneous and successive combination in reflex action.

Simultaneous combination. If the spinal cord of a dog is cut through in the cervical region below the level of emergence of the phrenic nerve and sufficient time allowed for recovery, gentle stimulation of a saddle-shaped area of the dorsal trunk causes the hind limb on the side stimulated to execute a vigorous rhythmic movement which tends to bring the claws towards the part of the trunk stimulated (fig. 38). The reaction is obviously purposeful and designed to remove the irritant stimulus, e.g., a flea. If, for purposes of study, an "electrical flea" is devised consisting of an entomological pin through which an electric current passes, the characteristics of the response can be studied in greater detail. If at point A, a stimulus is applied which is just inadequate to evoke the reflex, and with the A stimulus still active a similar subthreshold stimulus is applied to point B several cms. distant from A, the two subthreshold stimuli may become effective and yield a typical scratch reflex. In terms of *c.e.s.* (ch. iv) the subliminal B stimulus has activated a sufficient number of neurons in the subliminal fringe (Denny-Brown and Sherrington, 1928) of the A stimulus to evoke a response: the one has "reënforced" the other. If stimulus A is adequate and stimulus B is also adequate, a stronger response will occur than when either point is stimulated alone. Both cases illustrate the principle of simultaneous combination. Sherrington (1906b) has studied in these special preparations the conditions affecting simultaneous combination such as the geographical distance between stimuli, the capacity of different types of stimuli to combine, etc., for which details the reader must consult his original paper. The principle of simultaneous combination also applies to *inhibitory* stimuli. Thus a pinch of the tail may combine with a prick of the thoracic skin to inhibit an extension reflex. Such illustrations might be multiplied indefinitely.

Successive combination. Owing to after-discharge in certain end organs and to the time consumed in internuncial circuits of the spinal cord, subthreshold stimuli applied at a given point may alter the excitability of the final common path for a considerable interval (ch. iv). Consequently successive stimuli may reënforce one another, even though

separated by an appreciable time interval. Thus in the scratch reflex if stimulus A, inadequate to excite alone, is applied to the skin, and shortly thereafter a similar stimulus B is applied at another point, the combined effect may be sufficient to evoke the scratch reflex. The threshold, in other words, of some neurons has been sufficiently altered to make stimulus B effective. The significance of successive combination is obvious when one considers the more usual forms of stimulation evoking the scratch reflex; thus it is generally a *moving stimulus* such as insects moving through the fur. In Sherrington's earlier discussion of successive combination he referred to the phenomenon as "immediate induction" which has wide applications in other branches of sensory physiology, particularly in the case of the retina where moving objects may evoke a visual sensation, whereas the same object fails to do so when stationary.

ANTAGONISTIC REFLEXES. Antagonistic stimuli may compete simultaneously for the final common pathway, but since the final common path cannot be occupied simultaneously by two reflexes of opposed effect, one or the other must be "prepotent." Thus when two stimuli which alone would evoke dissimilar reflexes are simultaneously applied to a spinal animal, one gains ascendancy. The outcome of the rivalry depends upon a number of circumstances: (i) the nature of the reflexes, (ii) the intensity of the several stimuli and (iii) the duration of action of the reflex. If, for example, stimuli for the scratch reflex and for the flexion reflex of the hindlimb are simultaneously delivered, the flexion reflex would generally appear to the exclusion of the scratch reflex, since the flexion reflex is a nociceptive reaction. In Sherrington's terminology the nociceptive reflexes are "prepotent" since they protect the body from danger, and consequently displace all other types of reflex competing for the final common pathway. The flexion reflex similarly displaces extensor reactions essential for the maintenance of body posture. Because of this an animal (or human being) wounded in the foot quickly "doubles up" and falls to the ground, since a painful stimulus inhibits his extensor reflexes.

When antagonistic reflexes are of approximately equal strength the one which succeeds in commanding the final path will depend upon the relative intensity of stimulus. Thus the flexion reflex generally displaces the scratch reaction. If, however, the stimulus evoking the scratch reflex is particularly strong, and the nociceptive stimulus weak, the

scratch reflex may persist and thus exclude flexion. The duration of a reflex also influences the outcome of rivalry. If the scratch reflex has been in operation for a considerable period of time, it is easier to divert it by a nociceptive stimulus than at the onset of the scratch reaction.

Successive induction. If antagonistic reflexes take command over the final common path in rhythmic succession, as in the act of walking, one reflex facilitates the subsequent use of the final path by the antagonistic reaction; this important principle of reflex action Sherrington has designated "successive induction." Successive induction no doubt plays an important role in all rhythmic movements of the nervous system, especially walking and galloping. Thus, when a leg is lifted from the ground, a flexion reflex is in operation. When it is replaced on the ground, the positive supporting reaction and stretch reflexes combine to bring out an extensor contraction whose appearance is facilitated by the fact that the flexor reflex had dominated the final common path immediately before.

Another type of integration carried out in the spinal cord is an intersegmental reaction by means of which the fore- and hindlimbs are brought into harmonious rhythmic movement.

INTERACTION OF FORE- AND HINDLIMBS. In animals having quadrupedal progression, ancient and well developed reflex movement patterns involving all four extremities are demonstrable in the spinal state. Whenever the flexion reflex occurs in one hindlimb, an extension reflex develops in the opposite hindlimb; concomitant reactions also occur in the forelimbs and vice versa (fig. 39) and these confer a definite attitude or "reflex figure" upon the animal (Sherrington, 1906a, p. 164). When a flexion reflex is evoked in one hind extremity, the ipsilateral forelimb extends, and the contralateral forelimb becomes flexed (Pi-Suñer and Fulton, 1928). These reactions can be obtained both from the exteroceptive and from the proprioceptive reflex zones and are most vigorous in response to nocuous stimulation. The significance of the reaction is obvious since it evokes a reflex figure that permits the animal to maintain its balance, *i.e.*, the ipsilateral forelimb is extended as is the contralateral hindlimb, so that the animal is supported and will not topple to one side. Like the flexion reflex, the reaction has an obvious purpose. In animals that hold themselves upright, there is a similar interaction between the forelimbs and the hindlimbs, but the effects are less readily demonstrated because of the greater degree of spinal shock.

Schiff-Sherrington phenomenon. Further evidence of interaction between the fore- and hindlimbs has been given by Ruch and Watts(1934) and Ruch(1936)in an analysis of the Schiff-Sherrington phenomenon. When the spinal cord of a decerebrate cat is transected in the midthoracic region, the forelimbs exhibit an immediate accession of rigidity. This is not due to the irritation incident to the transection, since it still

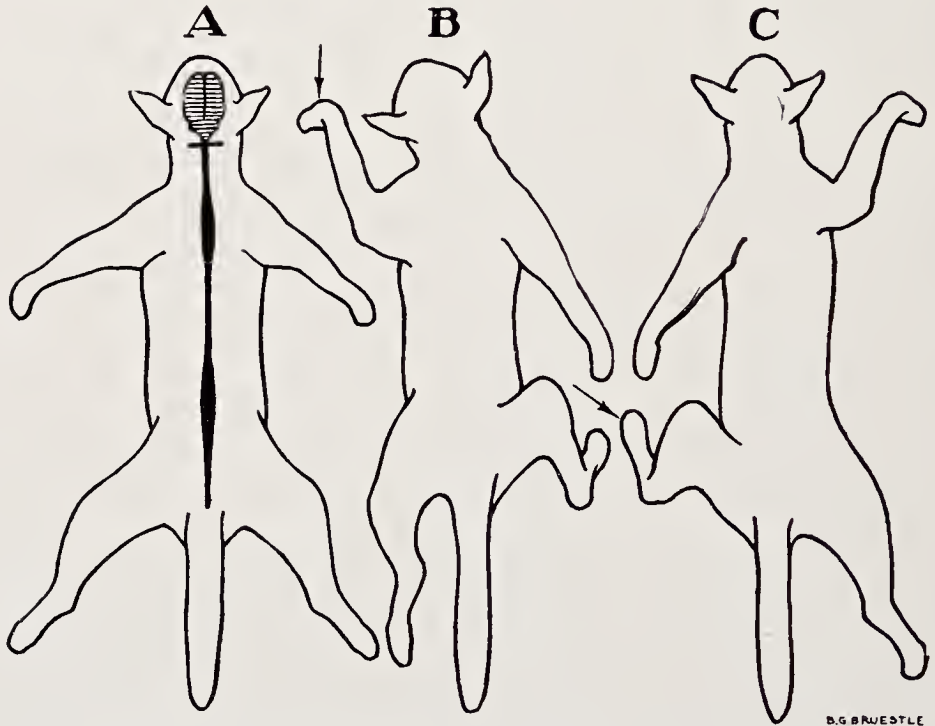


FIG. 39. Reflex figure of high spinal animal, showing postures assumed on stimulating extremities. Note influence of hindlimb on forelimb and vice versa(after Sherrington, 1898b).

occurs when the cord is functionally severed by cold(cold-block)or by novocaine. The effect furthermore is not abolished by section of dorsal roots caudal to the intended transection; neither does such root section induce the phenomenon. This cephalad effect arises, therefore, in the spinal cord through reflex circuits that are independent of dorsal root innervation. Cephalad effects can also be demonstrated in the lumbar segments of a spinal cat by again severing the cord between them and the sacral segments. In these circumstances the knee jerk(mediated by lumbar segments iv and v)becomes promptly augmented, as does the resting extensor posture of quadriceps.

VISCERAL REACTIONS

The isolated spinal cord is also capable of mediating large numbers of visceral reflexes after the symptoms of spinal shock have passed off. In the lower forms most of the visceral reactions are present within a few minutes after spinal transection, but in the higher forms, including man, intervals varying from some hours to several weeks may elapse before the visceral responses can be demonstrated. The classical account of the visceral reactions of spinal animals which has never been superseded is that of Sherrington published in 1900 in Schäfer's *Text-book of physiology* (1900b). Many of the following details have been taken from this source, being supplemented, when necessary, by more recent work.

SEXUAL FUNCTIONS — Female. Contractions of the uterus in response to manipulation of the sexual skin, clitoris and vaginal orifice can readily be demonstrated in the spinal bitch. Vaginal secretions are probably also reflexly evoked in this manner. In the female primate section of the spinal cord interrupts the menstrual rhythm in such a way that, irrespective of the time the cord is severed, a normal menstrual period follows within 5 to 6 days (macaque, van Wagenen, 1933). Thereafter the menstrual periods succeed one another at the usual intervals. Sherrington and Goltz (1874) both succeeded in impregnating a spinal bitch which delivered herself after the usual period of gestation of a normal litter of puppies. Goltz and Ewald (1896) also impregnated a bitch after the cord had been completely removed.

Male. In a chronic spinal dog and cat, and also in monkey and man, erection of the penis quickly occurs on gentle manipulation of the skin of the thigh or the genitals themselves. Persistent priapism may develop immediately after the cord is cut, probably owing to vasomotor release. This undoubtedly accounts for the state of satyriasis so often seen in hanged criminals. Ejaculation may also be brought about by gentle masturbation, especially in dogs, and it has also been described in man. Sherrington pointed out that in the male spinal dog manipulation of the genitalia also caused the posterior quarters to curve downwards, thus thrusting the penis forward into the copulatory position. In a recent study of this phenomenon, Dusser de Barenne and Koskoff (1932, 1934) found that the male cat assumes a similar posture immediately after spinal transection, it being especially prominent when the animal is prone with adductor muscles slightly stretched. In these circumstances a

strong flexor rigidity develops in the hindlimbs, which they interpret as a part of the copulatory pattern. The reactions are most conspicuous in the male during the breeding season. In this connection the early observations of Spallanzani on the copulatory posture of the male frog during the breeding season are of interest. He reported that, once the posture developed, actual decapitation of the frog did not destroy it. Indeed, the reflex could be maintained by a few isolated segments of cervical spinal cord with all of the rest of the nervous system destroyed above and below it. It is clear, therefore, that the basic patterns of sexual behaviour are laid down in the spinal cord.

MICTURITION (See p. 216 and ch. xx).^{*} The act of emptying the urinary bladder involves a complex sequence of reflexes integrated, like many other "chain" reflexes, at various levels of the cerebrospinal axis. To avoid repetition in later chapters the physiology of micturition, which is primarily a spinal reflex, will be considered here, although full treatment will to some extent anticipate information concerning the higher centres recorded later.

BLADDER INNERVATION —(a) *Motor*. The urinary bladder and urethra receive motor innervation from three sources: the sympathetic, parasympathetic, and somatic outflows. (i) *Sympathetic* innervation, as indicated in figure 40, comes in the cat, and possibly also in man and monkey, from L₂, L₃ and occasionally also from L₄. The preganglionic fibres pass to the inferior mesenteric ganglion and postganglionic fibres originate and pass via the hypogastric nerves to the bladder wall and also to the urethra. (ii) The *parasympathetic* component reaches the bladder and urethra via the pelvic nerves (n. erigens), which originate from sacral levels 1, 2 and 3. (iii) *Somatic* volitional innervation reaches the striated musculature of the urethra and bladder sphincters via the pudic nerves, which take origin from the first two sacral roots.

(b) *Sensory*. The bladder also has an extensive sensory innervation conveyed by the pelvic and pudic nerves (including pain); pain fibres also pass to the spinal cord via the hypogastric nerves. The pelvic nerves supply the stretch-afferents of the bladder wall (Talaat, 1937), while the pudic nerves carry a large proprioceptive innervation from the striated muscles of the bladder sphincters.

BLADDER REFLEXES. Attempts to unravel bladder physiology through nerve stimulation have proved highly unsuccessful since mechanisms normally responding in sequence are thrown simultaneously into activity

^{*} The physiology of micturition has been fully covered in the recent monograph of Langworthy, Kolb, and Lewis (1940), but reference should also be made to the classical papers of Barrington (1914, 1921, 1928 and 1931); and to studies on the human bladder by Head and Riddoch (1917), Denny-Brown and Robertson (1933) and Learmonth (1931). Attention of students is also directed to the excellent chapter on the urinary bladder by Walter S. Root (1941).

by nerve stimulation. In general, however, it is probable that the sympathetic tends to relax the bladder wall when stimulated, whereas parasympathetic fibres cause contraction (Learmonth, 1931). When the bladder becomes distended a sequence of reflexes develops which leads ultimately to the expulsion of fluid. The basic reflex pattern is laid down

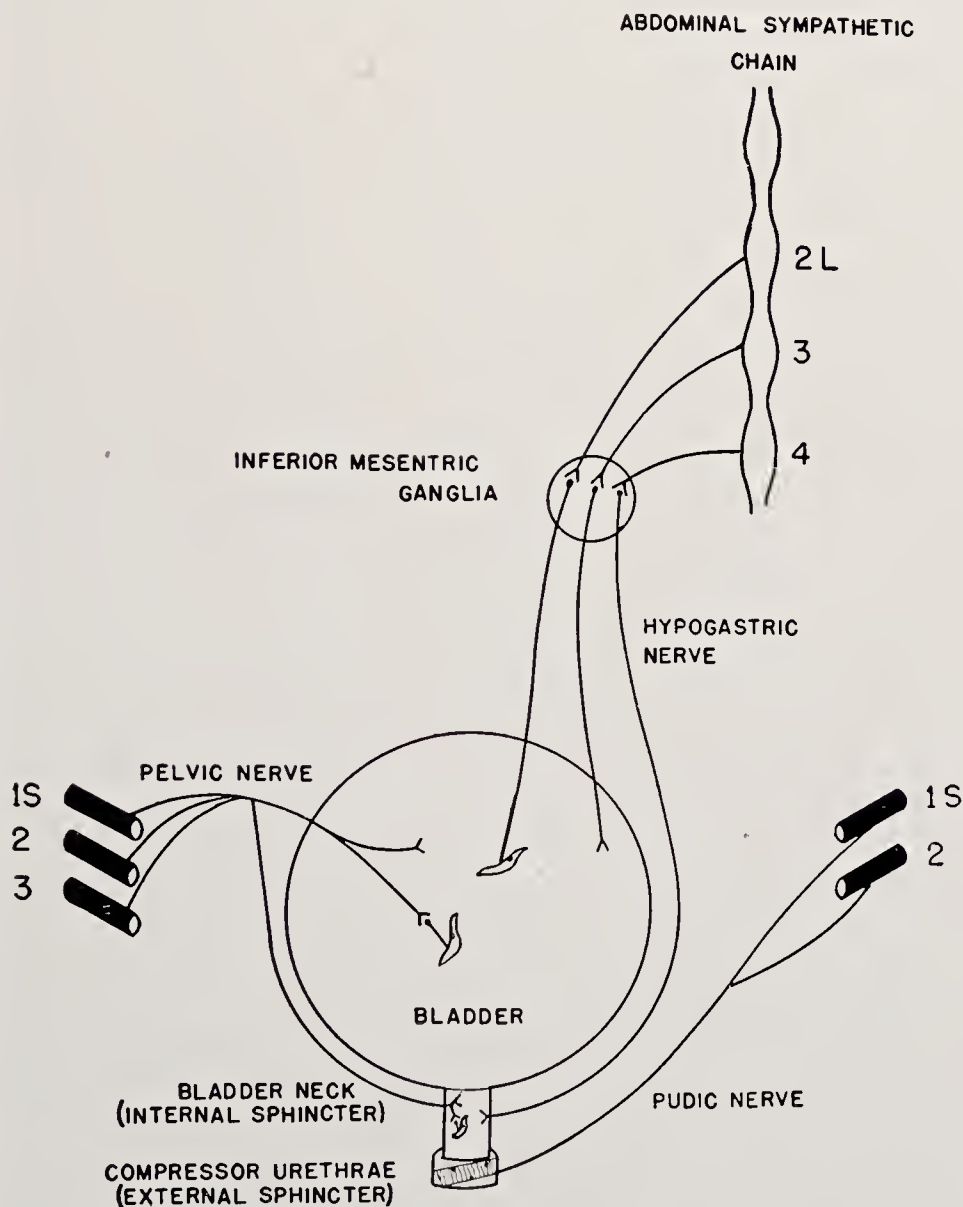


FIG. 40. Diagram of bladder innervation after Root(1941).

in the spinal cord, but the normal volitional act of micturition depends upon integration emanating from the hypothalamic area, as well as from the cerebral cortex. Contraction of the bladder can be evoked by stimulation of the motor area of the cerebral hemispheres(see ch. xxii).

Barrington has described a series of six discrete and separable reflexes associated with bladder emptying. They are summarized in the following table.

The Bladder Reflexes(from data published by Barrington)

REFLEX	EXCITING STIMULUS	AFFERENT	EFFERENT	RESPONSE	CENTER
1	Distend bladder	Pelvic	Pelvic	Blad. contract.	Hind-brain
2	Fluid in urethra	Pudic	Pelvic	Blad. contract.	Hind-brain
3	Distend post. urethra	Hypogast.	Hypogast.	Blad. contract.	Cord
4	Fluid in urethra	Pudic	Pudic	Relax urethra	Cord
5	Distend bladder	Pelvic	Pudic	Relax urethra	Cord
6	Distend bladder	Pelvic	Pelvic	Relax post. 3rd urethra	Cord

As the bladder becomes gradually distended with fluid a certain point is reached at which the detrusor muscle contracts; the bladder neck, the compressor urethrae muscles then relax and the bladder contents become expelled. Reflex contraction of the detrusor is essentially a stretch reflex depending upon intravesical pressure rather than upon volume since, if the bladder wall is rapidly stretched, it is thrown into reflex contraction more rapidly than when filled by gradual increments. The act of micturition is facilitated by the secondary reflexes indicated in Barrington's table. Reflex 1, bladder contraction from distension, has already been mentioned. Reflex 6, relaxation of the urethra, follows and this is associated with reflex inhibition of the compressor urethrae(reflex 5). The act of micturition is further facilitated by the passage of fluid along the urethrae(reflex 2), which augments bladder contraction, as possibly also does distension of the posterior urethra(reflex 3). The importance of Barrington's third reflex has been questioned by Denny-Brown and Robertson(1933). Talaat(1937) detected action currents in the afferents of the hypogastric nerve only when the bladder was distended to a degree that in man would cause pain or acute discomfort.

Bladder reflexes in spinal animal. The state of the bladder in a spinal preparation, be it man or animal, is similar to that of an organism with an intact nervous system after spinal shock has passed off, except for the fact that reflex emptying is never complete and the residual urine is prone to become infected. Immediately after spinal transection, especially in man and monkey, the Barrington reflex sequence is disturbed

and, while the bladder may contract reflexly, the relaxation of the sphincters fails to occur and a state of acute retention of urine supervenes. For this reason it frequently becomes necessary to catheterize the bladder of human beings (as well as of animals) following spinal injury, until the normal coordination of the reflex act of micturition becomes once more reestablished. Failure of coordination between reflexes occurs with lesions of the hypothalamus, and more particularly after destruction of the motor area of the cortex bilaterally which generally leads to relaxation of the bladder sphincters with resulting incontinence. The bladder sphincters in a spinal animal become spastic, whereas following cerebral injury they tend to suffer a flaccid paresis.

NERVE LESIONS — *Pelvic nerves.* Bilateral division of the pelvic parasympathetics to the bladder results in urinary retention caused by relaxation of the bladder wall and spasm of the bladder sphincters. An animal with the pelvic nerves cut may become seriously distended, but passive pressure on the abdomen may force the sphincters, usually, however, only with difficulty (Langworthy, 1940).

Pudic nerves. Section of the somatic innervation of the urethra and sphincters causes paralysis of the sphincters and persistent urinary incontinence. It is evident, therefore, that the integrity of the pudic nerves is essential for the maintenance of normal urethral and sphincter tone. Similar lesions in man cause little difficulty in micturition, owing possibly to accessory sphincter innervation through the pelvic nerves (Learmonth, 1931).

Sacral dorsal nerves. Deafferentation of the bladder through section of the dorsal roots in the sacral levels causes symptoms similar to those seen in patients with tabes. The bladder is relaxed, retention supervenes and complete expression of urine becomes impossible.

Hypogastric nerves. Section of the hypogastrics causes increased frequency of urination both in cats and man, although the symptom tends to be transient in human beings. The hypogastrics are not essential for the normal act of micturition, but if severed, there is diminution of the pain and discomfort associated with overdistension of the viscus.

Cerebral control. It is evident from personal experience that the urge to micturate can normally be restrained through volitional effort. This is associated with some degree of inhibition of contraction of the bladder wall, volitional closure of the external sphincter and concomitant contraction of the perineal muscles. It is generally believed that the absence of inhibitory control in infants can be correlated with lack of development of cerebral centres, and an adult human being after a bilateral lesion of the sacral motor representation in the cortex develops a bladder identical with that of a baby. Woolsey and Brooks (1937) find that following cortical extirpation the volume of fluid passed at each micturition becomes virtually constant, an observation suggesting that the cerebral cortex causes variation of the reflex threshold of micturition.

DEFECATION. Immediately after the cord is cut, the anal, and also the vaginal sphincters, may exhibit a patulous relaxation with tendency towards prolapse. The tone of the sphincters, however, generally recov-

ers within a few days, and after several weeks the rectum begins to empty itself automatically. During the first days after spinal transection, there is generally great increase in peristalsis of the gut, and a tendency towards watery stools with a profusion of mucus; but the characteristics of the gastrointestinal disturbances in spinal dogs have never been thoroughly analyzed. The great increase in peristalsis observed by Claude Bernard(1858)and others after spinal transection does not occur when the brain stem is severed above the vagus nucleus. Section of the vagus tends to cause stasis in the gut and impairment of digestive processes (Ferguson, 1936). The act of defecation is accompanied by movements of the hindlimbs and tail similar in character to those made in normal defecation by the dog, *i.e.*, the posterior end of the body is raised on the extended hindlimbs, the tail is raised, and after expulsion of the materials in the rectum there follow the usual movements of *nettoyage* of the hindlimbs.

Denny-Brown and Robertson(1935)in their study of nervous control of defecation find that the act of defecation may still occur in man after complete destruction of the sacral and lower lumbar segments. The adequate stimulus for the act is a stretch of the wall of the rectum; this serves to initiate peristaltic contraction that leads to relaxation of the anal sphincter. The nervous mechanism involved in the reaction lies in the peripheral nerve plexus surrounding the walls of the rectum. The mechanism, however, is subject to influence from the spinal cord and is depressed after spinal transection, during which time the anal sphincters abnormally relax. Cutaneous stimulation of the sacral dermatomes may serve to initiate reflex defecation in spinal man and bladder contraction may be accompanied by simultaneous defecation. The sympathetic nervous system is not essential for these reflex effects, although it is probably capable of depressing them.

VASOMOTOR REACTIONS. Immediately after spinal transection, the systolic blood pressure falls conspicuously, sometimes as low as 40 mm. of mercury. Associated with the fall is a marked dilatation of the peripheral blood vessels. During the first days after a transection in dog or monkey, the level of the blood pressure fluctuates, the changes being often unpredictable, as was originally pointed out by Dittmar(1873). During the early days, moreover, it is impossible through stimulation of an afferent nerve situated behind the lesion to cause any change in the level of blood pressure. However, vasopressor reflexes eventually return along with somatic skeletal reflexes. Thus Sherrington(1906a, p. 242)was able in the spinal dog 300 days after transection at the eighth cervical level to obtain a rise from 90 mm. Hg to 208 mm. Hg, on stimulating the central end of a digital nerve to

the hindlimb. Recent studies of Krogh and others indicate that the vascular release, following spinal transection, is one affecting both the arterioles and the capillaries. Sahs and Fulton(1940), who studied the return of autonomic spinal reflexes in monkeys, found that sweating, reflex vasoconstriction(crossed cooling response)does not return in the macaque until after many somatic spinal reflexes. In five illustrative cases sweating returned on days 14, 12, 14, 5 and 22, respectively, and crossed cooling on days 42, 26, 52, 17, and 39.

In an important study of the relation of vascular reflexes of spinal animals to emotional states, Sherrington(1900a), prior to Pavlov, described a conditioned reflex(noise of an inductorium), which caused the dog's heart to be inhibited. The inhibition was mediated through the vagi and, after these had been severed, cardiac inhibition disappeared, but the animal's emotional reaction to the sound of the inductorium continued.*

Sweating. Sudorific responses also occur in spinal animals; generally, however, they do not appear until some weeks after spinal transection, as will be seen in the following account of spinal man.

SPINAL MAN

Although injuries of the spinal cord have long been a subject of clinical investigation, it was not until the Great War that opportunity presented itself to study a large number of uncomplicated cases. Undoubtedly the most significant and painstaking studies were those of Head and Riddoch(1917)and the account which follows is based largely upon their work.

COMPLETE TRANSECTION OF SPINAL CORD. Throughout the animal scale it is a striking fact that immediately after spinal transection the flexor reflexes, at first depressed, *always reappear before the postural extensor reflexes*. Thus, in the cat, although flexor reflexes may be elicited soon after spinal transection(ch. iv), it requires several days or weeks before stretch reflexes can be obtained from quadriceps or soleus(dog; Denny-Brown and Liddell, 1927a). The limbs during this period are held in persistent flexion, and any slight irritation of the pads of the feet provokes marked flexor spasm(ch. vi). In monkeys, after spinal transection, extensor responses are abolished for an even longer period(Fulton and Sherrington, 1932), the absolute interval varying from animal to animal and with the species of monkey(see below).

In man, after complete spinal transection, extensor responses may never return, although in certain instances they appear to do so in a poorly sustained form. For a period of 3 to 4 weeks after a complete transverse lesion even flexor responses are often unobtainable, owing to

* This observation formed the basis of Sherrington's(1900a)well known objection to the James-Lange theory of the emotions.

the profound shock incident to such a lesion. The first sign of reflex activity to appear in spinal man is a slight up-going of the great toe when the sole of the foot is scratched. In one of Head's cases (described below), this appeared for the first time on the 22nd day and was associated with a simultaneous slight contraction of the hamstring muscle. Previously there had been no sign of response in the hamstring and none in the toe, the two reflexes appearing at the same time. This indicates that *the sign of Babinski is part of a generalized flexor reflex* (cf. ch. vi). The sequence of events in the recovery of a human being from a complete spinal transection may be conveniently set forth by summarizing one of Head and Riddoch's cases. The following was first described in great detail by Riddoch (1917b) and subsequently studied jointly by Head and Riddoch (1917).

CASE 1. *Complete transection of spinal cord at Th 6; flexor responses on 22nd day and knee jerks on 25th day; crossed extensor responses on 45th day. "Mass" reflexes with facilitation of bladder contraction by reflex activity. Paroxysmal sweating.*

Lieut. M., aged 28, was struck in the mid-thoracic region of his back by a shrapnel bullet on Aug. 6, 1916. The projectile was removed on September 8th, and the spinal cord was observed to be completely severed between the fifth and sixth thoracic segments and its two ends were separated by 2.5 cm. The patient was kept under observation for a period of 325 days.

11th day. There was complete loss of motion and sensation of both superficial and deep reflexes below the level of the sixth rib. Motion, reflexes and sensation in the arms were normal. There was no sweating below the lesion. The sphincters were tonic and there was complete retention of urine.

22nd day. Motion and sensation continued unchanged and knee and ankle jerks and abdominal reflexes all absent. "For the first time on this date upward movement of the toes was noticed on scratching the sole of the foot. Hamstring contraction had not been obtained previously on plantar stimulation; but with the first appearance of this upward toe movement the hamstrings could be felt to tighten and contraction also appeared in the anterior tibial group of muscles. The receptive field for the reflex was limited, at this stage, to the soles of the feet, and the threshold was lowest on the outer side. No crossed response of any kind could be obtained." Urinary retention was no longer complete though catheterization was still necessary. He had begun to have unilateral sweating on the left side of his head, neck and left arm, but no sweating below the level of the lesion.

25th day. Slight periodic movements were noticed from time to time in both legs; these consisted of upward movements of the great toes with contraction of the flexor muscles at knee and ankle. For the first time tapping of the right patellar tendon evoked a contraction of the quadriceps. Micturition had become more frequent and more urine was voided at a time.

33rd day. The shrapnel bullet was removed from the body of the sixth dorsal vertebra. The patient made an excellent post-operative recovery and during the next few weeks a gradual increase occurred in the intensity of the involuntary movements; they were always flexor in type, with up-going of the great toe, the

dorsiflexion of the foot at ankle, and there was vigorous flexion of both knee and hip. With these movements there was some adduction of the thigh and spasm of the rectus-abdominis muscles. Occasionally the limbs became flexed alternately.

45th day. For the first time during a flexor spasm of one hindlimb there occurred weak *crossed extensor* contraction (Phillipson's reflex) in the opposite quadriceps, but it was too weak to produce movement of the extremity. The crossed reflexes, however, gradually increased in magnitude and by the 259th day there was moderate extensor movement of the crossed hindlimb with each flexor spasm of its fellow limb. Within a few weeks after his operation, the patient's neurological status became stationary and continued virtually constant as follows:

Motion. There was no voluntary power below the level of the sixth rib, and all involuntary movements were invariably flexor in type on the side stimulated. No manipulation could be found which would produce a primary extension of the stimulated limb. Crossed extensor contraction, however, increased in vigour during the first year after his injury. Occasionally spasms of involuntary movement began with the muscles of the abdominal wall and spread rapidly to the lower extremity.

Resting posture (tonus). This was described in Head and Riddoch's words as follows: "When the lower extremities were not in motion, the tone of the physiological flexors was below normal, but that of the extensors was relatively much less developed. During contraction, however, the tone of the flexors was greatly raised, whilst the tone of the extensors of the limb was greatly diminished. When the extensors were contracting, the converse was true; a flexion reflex was induced and the crossed extensors contracted; their tone was increased, but it was never so great as that of the contracting flexors."

Reflexes. As already mentioned, the first reflex to return, and the predominating reflex throughout the whole period of observation, was a flexor withdrawal of the lower extremity, evoked by almost any stimulus, but was particularly vigorous in response to a nociceptive stimulus. It was obtained from any part of the lower extremity, the reflexogenous area extending from the abdomen to the foot, the threshold being lowest on the plantar surface; scratching the abdomen or lower extremity or even grasping the foot or muscles of the thigh would invariably evoke a flexor response. Strong contraction of the rectus abdominis muscles was evoked by stimulation of the glans, external genitalia, or skin of the perineum. This also caused a vigorous cremasteric reflex. *Knee* and *ankle jerks* grew more and more exaggerated with time, but there was no sustained stretch reflex and ankle and patellar clonus died away after one or two rapidly diminishing jerks.

Sensation. Touch, pain, temperature and position sense remained completely absent below the level of the sixth rib. A tuning-fork was not appreciated below the level of the ninth rib. The patient seemed to be aware of vague discomfort when his stomach was distended, indicating that the sensory supply to the stomach comes in part from segments above the sixth dorsal level and also from the vagus nerve. He did not recognize distension of his bladder, had no desire to pass urine and experienced no relief when the bladder was emptied.

Bladder. Several months after his injury the patient had observed that he could, on awakening, prevent the inconvenience of involuntary micturition during his dressing by calling for his bottle, and scratching his thigh, which invariably invoked prompt involuntary micturition. In analyzing this phenomenon it was found on a given day that the bladder emptied involuntarily after 425 cc. of fluid had been run in through a buret. On this occasion he passed 420 cc. and nothing was

recovered by pressure. Fluid was again run in and evacuation occurred promptly; in this instance, he passed the whole amount. On the next occasion flexion reflexes were evoked rhythmically from the right foot, while the fluid was being run into the bladder; evacuation then occurred when only 160 cc. had been admitted. Similarly on another occasion, when 400 cc. had been passed into the bladder without concomitant reflex activity, a subsequent flexor reflex caused partial extrusion of the fluid.

Sweating. On the 61st day sweating below the level of the lesion became noticeable, and there was still sweating above the lesion (ceasing on the 90th day above, but still present below the lesion). On the 144th day it became apparent that hyperidrosis was precipitated by catheterization and by subsequent manipulations incident to washing out the bladder; administration of an enema, moreover, produced most profuse sweating. On the 259th day the following circumstances were found to precipitate sweating below the lesion: (i) spasms of the leg, especially repeatedly induced flexion reflexes, (ii) an enema, (iii) catheterization, (iv) change of temperature, *i.e.*, when being lifted out of his bath sweat poured from his whole body, especially from his lower extremities, but there was no change of pulse or pupils during such hyperidrosis. Oddly enough, during attacks of sweating the patient became aware of the sensation of drumming in his head or a feeling of "fat-headedness."

Defecation. Reflex defecation was initiated by stimuli similar to those which induced sweating.

Other cases of abrupt thoracic spinal transection in man have run a closely similar course (Oldberg, 1938). It is evident that the receptive field for the flexion reflex was at first limited to the soles of the feet, the threshold being lowest on the outer plantar surface. No crossed response of any kind could be elicited during the first weeks. Gradually the flexor responses became more and more vigorous, involving an increasing number of muscles in the flexor group, and the receptive area gradually spread up both limbs to the pelvic region. *After recovery from shock has occurred, one can obtain the Babinski response almost as well from the thigh of a paraplegic man as from the plantar surface.* Scratching, pricking or pinching are more effective stimuli than gentle pressure. Evidently the stimulus, which, in an intact man, would give pain, is the adequate stimulus *par excellence*.

In the case just described, *extensor* contraction began to appear on the 25th day in the form of a slight response to vigorous taps on the patellar tendon. There were no crossed extensor reflexes, however, during a flexor contraction on one side until the 45th day. Then during a vigorous flexor spasm, *e.g.*, of the right leg, there would be weak extensor response of the left leg (Philippon's reflex)—an exact prototype of the phenomenon which one so frequently encounters in spinal cats. During flexor contraction there was noticeable inhibition of the extensors on the same

side. Clonus and stretch reflexes were not sustained, because of the greater depression of extensors than of flexors in spinal shock. The paroxysmal sweating with flexion, bladder contraction, defecation, etc., all of which may occur simultaneously in spinal man, is a manifestation of the so-called "mass reflex." Sensory impulses, instead of being restricted to well defined channels as is the case when the higher centres are intact, spread diffusely throughout the spinal cord, especially along the more primitive pathways to the sympathetic and flexor centres. The physiological basis of these defensor reflexes has been particularly well expressed by Head and Riddoch (1920, p. 501):

"Uncontrolled flexion, on the other hand, as far as the lower extremities are concerned, still maintains its close relation with impulses, which would underlie pain or discomfort, if consciousness were present. The sole of the foot, even in man, must still be protected from injuries by stones and thorns, and the response is an immediate withdrawal of the limb that has been hurt. This is the essential flexor spasm, and it still retains many of the marks of its origin: it is more easily evoked from the front of the sole, and the most effective stimulus is a prick or a scratch. Such protective reflexes are the oldest in the phylogenetic scale, and, wherever they still remain in the human organism, betray their primitive origin. Although the movements they evoke are normally strictly under the influence of higher control, the reflex mechanism upon which this influence acts belongs to the more lowly centres in the nervous system."

INCOMPLETE LESIONS OF SPINAL CORD: BROWN-SÉQUARD SYNDROME. There is no more effective way of bringing before a student the chief facts of the anatomy and physiology of the spinal cord than by having him prepare an essay on the consequences of lateral semisection of the spinal cord in the cervical region. Although Galen carried out this experiment in antiquity, we are indebted to Brown-Séquard for the first detailed analysis of the effects produced by such a lesion. His studies were made at the Harvard Medical School in 1856-57, and he summarized the results of his observations some years later as follows: "In a spinal cord an alteration in a lateral half produces hyperaesthesia and paralysis of movement in the corresponding side, behind the place of the alteration (that is, caudal), and a loss of sensibility without the loss of movement on the opposite side" (*Course of lectures on the physiology and pathology of the central nervous system*, 1860, p. 111). Again on page 200 he says: "Below the decussation of the pyramids a lesion in(half) the spinal cord produces paralysis in the same side and anaesthesia on the opposite side." This is a simple statement of what is now known as the Brown-Séquard syndrome. A further symptom which was apparently not recognized by

Brown-Séquard, or at least it was not mentioned in this work, is the loss of position sense on the same side as the lesion.

A modified Brown-Séquard syndrome occurs in a very large proportion of cases of tumour of the spinal cord, because growths compressing the spinal medulla are seldom entirely symmetrical, and as a result one half of the cord becomes compressed before the other. Inevitably, therefore, there is an impairment of voluntary power on the side of the lesion with loss of position sense on that side, and pain, pressure and thermal sensibility become impaired on the opposite side of the body, since the tracts conveying pain, pressure and temperature cross soon after they enter the cord, while those (the posterior columns) responsible for position sense do not cross until reaching the medulla, and the descending motor pathways do not cross below the decussation of the pyramids.

Neurologists are more frequently called upon to diagnose and to interpret incomplete lesions of the spinal cord than they are to deal with complete transections, the latter being rare except in war time. It is, therefore, essential that they be able to interpret the complex picture which such cases often present.

The outstanding difference, from the point of view of reflexes, between a complete and an incomplete lesion of the spinal cord is the marked tendency toward extensor spasm when the cord is only partly divided. Instances of spinal paraplegia are seen with complete loss of sensibility below the level of the lesion and yet they may have marked extensor spasm if the limbs are manipulated, especially if the leg is elevated from the popliteal space. *This is an unfailing sign of an incompletely divided cord* and may be of value both in diagnosis and prognosis. The nature of the extensor spasm in these cases will be discussed in the next chapter.

The physiological explanation of the occurrence of extensor spasm in an incompletely divided cord is not altogether clear. The integrity of either the pyramidal tract or the vestibulospinal tract appears essential for the maintenance of extensor posture. Since the vestibulospinal and pyramidal tracts are some distance from one another anatomically, it seldom happens that both are completely divided in a partly severed cord. Cairns and Fulton (1930) have studied the question by producing lesions with small doses of radium emanation. In these circumstances the cord is injured gradually and, even if the lesion proceeds to a complete transection, there is invariably a stage of very marked hyperextension. With large doses of radium, the phase of hyperextension lasts only 6 to 12 hours and gradually passes over into a complete flexion paraplegia. Study of the degeneration produced by such lesions indicates that until the last trace of control from the pyramidal or vestibulospinal tracts is removed extensor reflexes continue to be exaggerated. In one instance they were able to destroy everything except a small part of the two vestibulospinal pathways. In this case, the animal's hind extremities remained in permanent extension. Since the radium was always applied to the dorsal surface of the cord, the first symptom in these animals was a loss of position sense, due

undoubtedly to involvement of the posterior columns. One of the last tracts to be involved was the vestibulospinal, owing to its position on the anterior surface of the cord. Similar observations have been made by Fulton, Liddell and Rioch (1930a), Ranson, Muir and Zeiss (1932), and Liddell (1934, 1936) in studies of incomplete surgical lesions of the spinal cord.

Before considering the significance of the various incomplete lesions which may occur in the spinal cord, some consideration must be given to the phenomenon of spinal shock itself.

SPINAL SHOCK

The depression of reflexes which follows spinal transection, in segments posterior to the lesion is a phenomenon encountered in all vertebrates, as well as in certain insects, but the phenomenon is most conspicuous in the primates where its intensity varies with cerebral development (see Ruch, 1942).

When a frog is decapitated, its spinal reflexes are temporarily depressed (see historical note above), being completely absent for several seconds and noticeably depressed from 2 to 3 minutes. Later the limbs are drawn up in the usual posture and the frog, on appropriate stimulation, may hop away much as would a normal animal. If the spinal cord of a cat is transected under ether anesthesia, all reflexes are transiently depressed for at least an hour, generally for longer periods (McCouch, 1924). In the dog, the initial depression is more striking than in the cat, being again most marked in the extensor muscles. Among the monkeys, there is considerable variation in the extent of spinal shock, but in all monkeys it is far greater than in the carnivores. Thus, both the flexors and extensors may exhibit complete depression of all reflex response for periods varying from several minutes to several days. Even the knee jerk, which in the spinal cat is never abolished, may be inelicitable for some hours or days following spinal transection (Fulton and Sherrington, 1932). Other reflexes are similarly abolished and some may never return. In the *Erythrocebus* group of monkeys, all reflexes are depressed but none of them abolished, whereas in the macaque, baboon and chimpanzee the reflex depression, especially in the chimpanzee, may be almost as great as or greater than that in man (Fulton and McCouch, 1937).

Numerous hypotheses have been advanced concerning the causes of spinal shock. It was thought at one time that the trauma of spinal transection might account for loss of reflexes; but since the depression arises in segments far removed from the level of transection, trauma as such is an unlikely explanation, the more so because reflex depression continues for periods of many months. Others have suggested that the fall in the blood pressure might disturb spinal reflexes, but this can scarcely be urged seriously since reflexes involving the suprasegmental parts of the brain are not affected by the generalized fall of pressure. The more re-

cent concept of spinal shock, first proposed by Sherrington(1898, 1906), and recently supported by Liddell(1934), suggests that the reflex depression is due to the sudden withdrawal of a continuous excitation ("facilitation") which normally occurs from suprasegmental levels. One asks at once, what descending pathways are responsible for the continuous excitation essential to prevent the onset of spinal shock. This can be investigated, provided one can employ some measurable index of spinal shock. Ballif, Fulton and Liddell(1925)observed that one of the

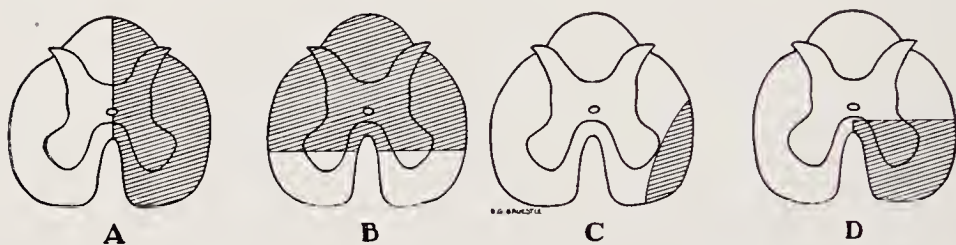


FIG. 41. Incomplete lesions of spinal cord, showing portion of ventral quadrant, integrity of which is essential for protection from spinal shock. A, Lateral semisection, causing spinal knee jerk on right side. B, Section of dorsal two-thirds, causing no spinal shock. C, Isolated lesion of ventral quadrant, causing no spinal shock(decerebrate preparation). D, Isolated lesion of ventral quadrant which caused marked symptoms of shock(after Fulton, Liddell and Rioch, *Brain* 1930, 53).

principal manifestations of the spinal state is an increased susceptibility to inhibition of all of the extensor reflexes, including the knee jerk. As indicated in chapter v, a series of knee jerks may be readily inhibited in a spinal animal by application of a single break shock to an ipsilateral sensory nerve. *The curve of recovery may be taken as an objective index of the depth of spinal shock in any given preparation*(figs. 26 and 27). Liddell has recently found that the recovery of the knee jerk from inhibition is more rapid in chronic spinal animals than in the acute. Indeed, when 200 days have elapsed following transection the rate of recovery from an inhibitory stimulus may be as rapid as that of a decerebrate preparation.

Following incomplete surgical lesions of the cat's spinal cord(Fulton, Liddell and Rioch, 1930)signs of spinal shock did not become evident until the ventral quadrant of the spinal cord was encroached upon; indeed, the dorsal two-thirds of the spinal cord could be cut through without causing the knee jerk to exhibit signs of spinal shock(fig. 41). If, however, the ventral third of the spinal cord was severed as a primary procedure, the knee jerk on the side of the lesion immediately showed

evidence of spinal shock. The flexion reflex also showed evidence of release when this part of the cord was damaged (Liddell, *et al.*, 1932; Forbes, *et al.*, 1923). Section of the posterolateral region of the cord, likewise influenced the flexor response. The principal descending pathway in the ventral quadrant of the spinal cord is the vestibulospinal. Attempts have, therefore, been made to destroy the vestibulospinal tract at its origin by making isolated lesions of the vestibular nucleus. If, after such a lesion, the cat were subsequently decerebrated, the knee jerks on the side of the lesion showed moderate signs of spinal shock and the flexors are released. Consequently it may be concluded that in the cat the important descending pathway which prevents the onset of spinal shock is the vestibulospinal and probably also the ventral reticulospinal which passes through the same region.

In man and higher primates, the situation is somewhat different, because of the dominance of the corticospinal system. In cat and dog lesions of the motor area, or destruction of the corticospinal system produces little, if any, depression of spinal reflexes. The bear, however, which has a more extensive corticospinal system, shows moderate reflex depression for several days (Fulton and Ferguson, 1933). In primates, lesions of the vestibulospinal system, if primary, produce only slight reflex depression, but destruction of the pyramidal tracts at their origin in the cortex causes conspicuous symptoms of spinal shock (McCouch, 1924). McCouch has introduced the useful procedure of first destroying the pyramidal tract at its origin and, after the animal has recovered, of then severing the animal's spinal cord; in this way analyzing the relative influence upon spinal shock of the pyramidal and the extrapyramidal motor systems. Fulton and McCouch, using this procedure, find that reflex recovery from spinal transection in the previously paretic limb is earlier than in the previously normal limb. The degree of difference between the two sides is directly related to the extent of representation of the part in the motor cortex (ch. xx), and is therefore greatest in the digital reflexes, especially the hallux, moderate in the knee jerk and virtually absent in the adductor jerk. In different animals the asymmetry of recovery is greatest in the chimpanzee, moderate in baboon and macaque, and scarcely perceptible in the red and green African monkeys whose cortical development is less extensive than the baboon and macaque. The optimal interval between cortical and spinal operation is directly related to the rate of recovery following the cortical ablation,

i.e., if the interval is too great, asymmetry of recovery will not be apparent.

If spinal transection follows an initial operation of lateral semisection of the cord at a higher level, the reflexes return first in the previously paretic limb, the asymmetry in these circumstances extending to the proximal joints as well as to the distal. It may be inferred from these observations that spinal shock in man is likewise due to interruption of descending pathways and that the corticospinal is probably more important than any other descending system. However, if the spinal cord becomes gradually blocked by a pressure from its dorsal surface, *e.g.*, a spinal cord tumour, the extrapyramidal projection in the ventral quadrant would, in some measure, protect the extensor neurons of the cord from the effects of spinal shock, as in the macaque and chimpanzee from which the pyramidal system had been removed. A study of incomplete lesions of the cord and of serial removal of the descending system throws light upon two common clinical syndromes: (i) paraplegia in flexion, and (ii) paraplegia in extension.

Paraplegia in flexion. As indicated in the discussion of spinal man, flexor reflexes may return, after complete spinal transection, with almost complete suppression of the extensor reflexes. A spinal human being may therefore pass into conspicuous paraplegia in flexion. The phenomenon is also seen in certain cerebral diplegias, but here the mechanism is not entirely manifest except that the pyramidal system on both sides must be destroyed before the flexed scissors posture develops (cf. ch. xx).

Paraplegia in extension is common with spinal lesions and bears evidence that the spinal cord has not been completely severed. The equivalent of paraplegia in extension has been reproduced experimentally by lesions involving the dorsal two-thirds of the spinal cord which leave the ventral quadrant intact (Ranson, Muir and Zeiss, 1932). Experiments on the cords of dogs and cats, however, are not strictly transferable to human beings, and further study is needed of incomplete spinal lesions, especially in the chimpanzee.

SUMMARY

The isolated spinal cord of any higher vertebrate is capable of combining elementary reflexes into movement patterns having obvious purpose. The process by which these combinations are effected is referred

to as "integration." The spinal animal gives evidence of integration in the somatic sphere as well as in the visceral sphere, the complexity of integration varying in different species, and, in any given species, with the interval after section of the cord.

The somatic reactions of the spinal animal illustrate the principle of the "final common path." Sensory impulses from each segment, involving nearly every type of receptor, influence ventral horn cells of one, or a few segments responsible for a given movement; in the intact nervous system the descending pathways from higher levels may also carry impulses to the same ventral horn cells. The motor units which have their origin in the ventral horn are thus the elements upon which all activity converges—hence the term "final common path."

Reactions evoking the same movement pattern are designated as "allied" reflexes: the stretch reflex and the positive supporting reactions both cause sustained extensor contraction and thus belong to the same category of reaction. Allied reflexes may dovetail simultaneously (simultaneous combination) or *seriatim* (successive combination).

Reactions of opposed effect, *e.g.*, a scratch reflex, and a flexion reflex, are designated as "antagonistic reflexes." When stimuli which alone would evoke dissimilar reflexes are simultaneously applied, rivalry occurs for control of the final common path, and the outcome depends upon which of the two is prepotent. In general, nociceptive reflexes dominate other forms of reaction. Like the allied reflexes, antagonistic reactions illustrate simultaneous and successive combination. In rhythmic reactions in which antagonistic reflexes alternate in controlling the final common path, *e.g.*, stepping reflexes, one reflex facilitates subsequent use of the final common path by the antagonistic reaction. This principle of facilitation of opposites is referred to as "successive induction."

Intersegmental reflexes in the hindlimbs affect the forelimbs in such a manner that a nociceptive stimulus applied to a hindlimb causes a predictable reflex figure involving extension of the ipsilateral foreleg and flexion of the contralateral.

The visceral reactions of the spinal animal include engorgement and secretion in the vagina in the female, erection of the penis and ejaculation in the male, and in both sexes gentle stimulation of the perineum induces the bodily attitude ordinarily assumed in copulation. The bladder innervation and reflexes are described; after a certain degree of distention, both in normal and spinal animals, the bladder, through a

series of coordinated reactions, empties itself reflexly; the act of defecation is also induced by distension of the rectum. After spinal shock has passed off, vasomotor reflexes can be evoked by stimulating any sensory nerve, but the level of the blood pressure fluctuates more than in a decerebrate animal. Sweating may similarly be evoked. The spinal animal, however, tends to exhibit stereotyped reactions, often inappropriate to the stimulus. Thus, the vigorous pressure on the thigh may simultaneously evoke flexion of the limb, defecation, emptying of the bladder, sweating and a rise of blood pressure. This diffusion of reaction is referred to as the "mass reflex."

Spinal man begins to show all of these reactions from three to six weeks after a midthoracic transection. The vigour of the response increases over a period of four to five months.

The initial depression of reflexes that follows spinal transection is referred to as "spinal shock." It is believed due to withdrawal of excitation from higher levels. In cats the spinal pathways essential for the prevention of spinal shock pass near the midline in the ventral quadrant and include the vestibulospinal system. In man and other primates the corticospinal pathways play a more important role in spinal shock than do the vestibulospinal.

Lateral semisection of the spinal cord gives rise to the Brown-Séquard syndrome, consisting of motor paralysis and loss of position sense on the side of the lesion with loss of pain and thermal sense on the opposite side.

IX

THE MEDULLA OBLONGATA: DECEREBRATE RIGIDITY

HISTORICAL NOTE

The phenomenon of decerebrate rigidity which is so conspicuous in a bulbo-spinal cat was no doubt observed by many early investigators, including Whytt, Rolando and Flourens, who all stated that animals may survive for varying periods following removal of the forebrain. The significance of the decerebrate posture, however, was not appreciated until Sherrington's well known paper was published on the subject in 1898 (preliminary announcement in 1897). For some 15 years prior to this Hughlings Jackson had been developing the concept of "release" of function in order to account for various manifestations of injury to the higher parts of the brain in man. The concept of release is implicit in some of the writings of Charles Bell (see Campbell Thomson, 1925), but Jackson was the first to give it general application. In hemiplegia, Jackson argued, the withdrawal of cortical influence and the accompanying loss of voluntary power led to the appearance of "positive signs" which result from overactivity of certain lower centres normally restrained by the cerebral cortex. Spasticity is not due, as some had supposed, to irritation from a lesion, but rather to "release" of lower centres from cortical control. Sherrington also interpreted the manifestations of decerebrate rigidity as "release phenomena," since they persist indefinitely; they cannot, he maintained, be attributed to irritation, for direct irritation of the cut surfaces of the brain stem does not increase the rigidity (actually it generally inhibits it). Since Sherrington's analysis of the mechanisms involved in decerebrate rigidity forms one of the principal milestones of modern Physiology, his arguments will be presented in this chapter much as they were originally set forth in 1898.

THE previous three chapters have been devoted to the reactions of spinal animals, and many of the patterns of response detectable in these preparations are also conspicuously present in the decerebrate, but here they exhibit a variety of delicate adjustments not found in the spinal state. In addition to this, the decerebrate, or bulbo-spinal, preparation exhibits many reactions foreign to the spinal animal; notable among these are respiratory movements, vomiting, sneezing and swallowing reflexes, a high and constant level of systolic blood pressure and a state of hyperactivity of the extensor muscles. The decerebrate animal, however, is incapable of maintaining its body temperature constant. It topples over if set on its feet, and it exhibits no spontaneous movements except in response to definite external stimuli. When Sherrington first discovered decerebrate rigidity, he asked himself the following questions: (i) Is

rigidity seen in all animals? (ii) What anatomical connections are essential for rigidity? (iii) What sensory pathways play a part in its maintenance? (iv) Can the rigidity be inhibited by stimulating other parts of the nervous system?

SHERRINGTON'S ORIGINAL ANALYSIS

When the brain-stem of a monkey is severed in the lower half of the medulla, the neck and tail droop, and if the animal is supported by the belly all four extremities hang flaccid, the reflex condition being identical with that of a high spinal animal. When, however, the cerebral hemispheres are removed by prepontine section of the brain-stem and the animal is suspended in the same manner, it hangs (Sherrington, 1898, p. 320) "with its fore-limbs thrust backward[in extension], with retraction at shoulder joint, straightened elbow, and some flexion at wrist. The hand of the monkey is turned with its palmar face somewhat inward. The hind-limbs are similarly kept straightened and thrust backward; the hip is extended, the knee very stiffly extended, and the ankle somewhat extended. The tail, in spite of its own weight, and it is quite heavy in some species of monkey, is kept either straight and horizontal or often stiffly curved upward. There is a little opisthotonus of the lumbosacral vertebral region. The head is kept lifted against gravity and the chin is tilted upward under the retraction and backward rotation of the skull." The condition in cat, dog, rabbit and guinea-pig is similar, and in all animals the effect on the forelimbs is much greater than on the hindlimbs. The effect generally comes on within a few minutes of transection, *i.e.*, as soon as the anesthesia has blown off, and usually reaches its maximum in an hour. Thereafter the rigidity continues without intermission for days. From the more recent observations of Bazett and Penfield (1922), it is clear that the rigidity of the decerebrate state persists indefinitely. Implicit in Sherrington's original description, but not emphasized until later, is the fact that *the rigidity is most intense in those muscles which normally counteract the effects of gravity*: the erectors of the tail, the retractors of the neck and the extensors of the extremities.

PHYSIOLOGICAL ANATOMY. Sherrington did not determine the encephalobulbar pathways whose interruption is essential for the appearance of rigidity, but he argued that *it could not be the pyramidal tracts, since after unilateral ablation of the forebrain, the rigidity developed on the*

homolateral side. By stimulating the remaining cerebral cortex, he was able to inhibit the homolateral rigidity, which, however, became more intense when both cerebral hemispheres were removed, and persisted after removal of the cerebellum (we now know that the removal of the cerebellum, or section of the superior cerebellar peduncles, actually exaggerates rigidity; cf. ch. xxv). On examination of the pathways of the cord essential for maintenance of rigidity, he disclosed the fact that section of the ventrolateral columns invariably abolished the rigidity in the fore- and hindlimbs of the same side. As a further argument that interruption of the pyramidal tracts does not play an important part, he pointed out that section of a lateral half of the bulb above the level of decussation of the pyramids abolished homolateral rigidity, which is also destroyed if the pyramidal tract is not sectioned in such a lateral lesion.

On the basis of these and other arguments, Sherrington suggested that the *vestibular nuclei* probably play an important part in the maintenance of decerebrate rigidity — an inference that has been borne out by many lines of evidence in recent years. In 1905, Thiele made successive coronal sections of the brain stem, beginning rostrally and proceeding backwards, noting that rigidity appeared only when the plane of section reached the posterior part of the thalamus. In 1914, Magnus determined the anterior limits more accurately (cat, dog and rabbit), finding that rigidity persisted until the plane of section passed between the two colliculi at an angle that excluded the mammillary bodies. This corresponds with Section III in Magnus' well known diagram (fig. 42). It will be seen that this section in the cat (and other animals as well) virtually excludes the red nucleus. Section II of this diagram, which excludes the small-celled part of the red nucleus and the anterior hypothalamus, is generally followed by rigidity. Rademaker (1926) has maintained that when the red nucleus of a cat remains intact, decerebrate rigidity is absent and the distribution of postural resistance is normal. Recent investigators (Ingram and Ranson, 1932 & Keller and Hare, 1934) have reported that isolated destruction of the red nucleus, or section of its descending projection, do not bring on rigidity when the central nervous system is otherwise intact; this is scarcely surprising, since the release manifestations of decerebrate rigidity are obviously additive, being greatest when all descending projections above the level of the vestibular nuclei are destroyed.

Section III (fig. 42), which represents the approximate level of Sherrington's original decerebration, accounts for the homolateral distribution of the rigidity in his unilateral decerebrations, since this passes just caudal to the crossing (decussation of Forel) of the descending fibres of the red nucleus. Magnus (1914) and Bazett and Penfield (1922) found that decerebrate rigidity persisted, as one proceeded caudally with coronal sections until Section V (fig. 42), which is just rostral to the vestibular nuclei, but Weed (1914) and more recently Keller (unpublished) have given clear-cut evidence that section of the brain stem near the caudal tip of the pons induces profound flaccidity, even though the vestibular nuclei are not encroached upon. The explanation is not wholly clear, but the observation itself has been repeatedly confirmed by Keller, both in acute and in chronic prepara-

tions of dogs and cats. Weed's original observation may be quoted (pp. 217-18): "In several cases, the brain stem has been transected just caudal to the caudal border of the inferior colliculi. The ventral border of such a section usually coincides with, or lies just cephalic to, the cephalic limits of the pontine nuclei. In all these cases there has been a short accentuation of rigidity, followed very quickly by a total loss of all rigidity with the assumption of a flaccid flexor attitude. In

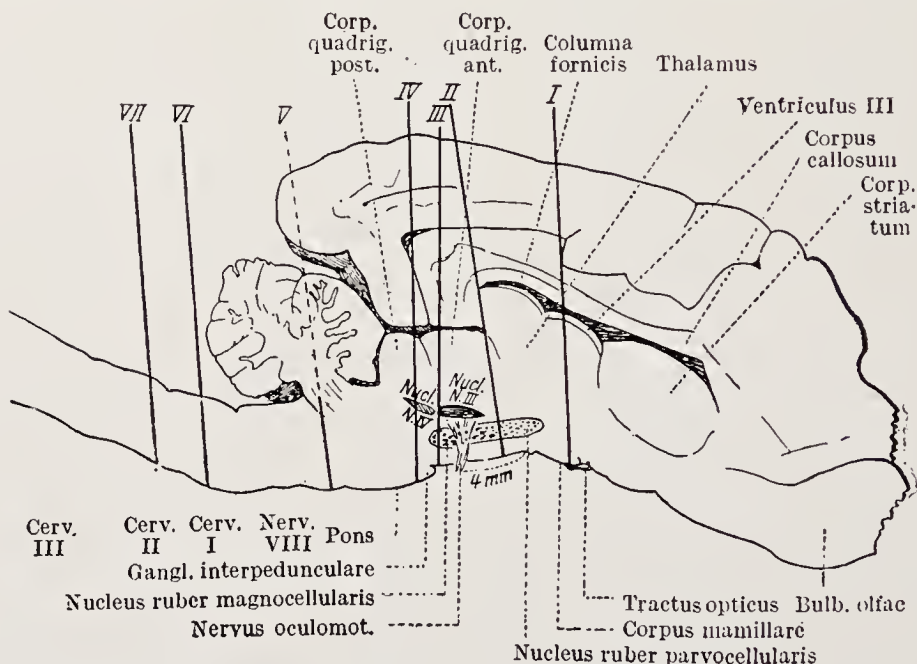


FIG. 42. Diagram of cat's brain, showing various levels of transection of brain stem used by Magnus, and also by Rademaker, in their analysis of decerebrate rigidity.

Section I. Thalamus animal; possessing heat regulation and normal posture.

Section II. Mid-brain animal. Posture normal, thermal regulation abolished.

Section III. Excluding red nucleus level brings on decerebrate rigidity.

Section IV. If unilateral gives homolateral rigidity.

Section V. Just above level of vestibular nuclei. Rigidity still present.

Section VI. Rigidity absent.

Section VII. Neck reflexes absent. True spinal animal.

some cases, the rigidity has remained for five minutes after the transection of the brain stem, but ordinarily it has entirely vanished within two minutes. In no case, however, has any rigidity been appreciably longer than five minutes after the time of transection of the brain stem. This disappearance of the rigidity after such a section delimits, with a degree of certainty, the source of the rigidities." Fulton, Liddell and Rioch (1930) established that isolated destruction of the vestibular nuclei abolishes rigidity in a decerebrate preparation induced by Section III.

Pollock and Davis (1923; see their summary of 1930) have thrown further light upon the problem of decerebrate rigidity through a new method of decerebration; this involves ligation of the carotids and the basilar artery (which is tied off by the buccal approach to the base of the medulla). This method produces, without mechanical trauma to the brain stem, complete suppression of function of the entire

forebrain, red nucleus and the greater part of the tegmentum and cerebellum, *i.e.*, the level of section approaches that of Section III of Magnus. The rigidity so induced is considerably more intense than that developing after section of the brain stem. The preparation has lent itself admirably to the study of the postural reflexes to be discussed in the next chapter, particularly the effects of labyrinthine extirpation.

Richter and Bartemeier (1926) have emphasized that decerebrate rigidity represents exaggeration of normal posture. This has been brought out through comparative studies; thus in the sloth, which normally hangs in the flexed posture, decerebrate rigidity is flexor in type in limbs, claws and trunk, and the animal will hang indefinitely after decerebration. Richter and Bartemeier find that the flexor rigidity is most characteristic when the red nucleus has been destroyed. In the case of man, one would expect, according to this thesis, that the lower extremities would be extended and the uppers flexed in decerebrate rigidity. This is actually true of the rigidities of cortical origin, but with complete decerebrate rigidity in man the upper extremities also become extended. This has led Russell Brain (1927) to suggest that the decerebrate attitude of a human being represents a reversion to the quadrupedal postural status of an earlier period of evolutionary history. Brain points out, moreover, that when a hemiplegic human being assumes the quadrupedal attitude, the upper extremities tend to become extended as in human decerebrate rigidity.

DORSAL NERVE ROOTS AND DECEREBRATE RIGIDITY. To return to Sherrington's line of argument, the next step he undertook was the elucidation of the influence of the sensory pathways. This led him to section of the dorsal columns of the spinal cord, as well as of the eighth nerve, but neither procedure influenced rigidity; however, severance of the afferent spinal nerve roots supplying a rigid extremity caused prompt disappearance of the extensor hypertonia (animal in pendant position).^{*} He argued that the effect can not be due to irritation, since it persists indefinitely, and, if the dorsal nerve roots are severed as a primary procedure, the rigidity fails to develop in the deafferented extremities on subsequent decerebration. Another incidental point was that section of the dorsal nerve roots prior to death considerably delays the onset of rigor mortis in the deafferented muscle. This was obviously significant, since

^{*} Although decerebrate rigidity as such is abolished by dorsal root section, Sherrington was careful to state that the flaccid muscle is accessible to other forms of reflex stimulation. Thus it becomes more readily responsive than before to crossed extensor stimulation; moreover, in 1910 Sherrington stated that the deafferented quadriceps responds also to tonic innervation from suprasegmental levels such as that caused by rotation of the neck (*cf.* footnote p. 163, ch. x). Pi-Suñer and Fulton (1927) studied the effects on the crossed extensor reflex of neck rotation in a deafferented quadriceps and at about the same time Bremer observed that the deafferented extensor was more responsive than normal to labyrinthine acceleratory reflexes. Thus, if an otherwise intact or a decerebrate cat with one limb deafferented is moved rapidly through space, it assumes, during the movement, a conspicuous extensor posture. These findings are in harmony with the conclusions of Pollock and Davis (1927, 1930b), who maintained that deafferentation does not completely abolish decerebrate rigidity (see also Ranson and Hinsey, 1929).

Sherrington had found that decerebrate rigidity itself hastens the onset of rigor mortis.

EFFECTS OF STIMULATION UPON DECEREBRATE RIGIDITY. Stimulation of many parts of the central nervous system demonstrably affect, and usually inhibit, decerebrate rigidity. Inhibition is obtained from the dorsal columns of the spinal cord, from the crura cerebri, and also from faradization of the pyramidal tracts (Fröhlich and Sherrington, 1902), and a particularly interesting form of inhibition arises from the anterior lobe of the cerebellum (cf. ch. xxv). Also from various parts of the cerebral cortex of the remaining hemisphere localized inhibition was evoked involving particular muscle groups, *e.g.*, elbow; from other areas, the extensors of the knee are inhibited (monkey). Sherrington pointed out furthermore that the areas giving inhibition of the extensors do not correspond with the areas which cause their contraction. All reactions from the cortex exhibit reciprocal innervation.

Even more interesting were the effects of stimulating *peripheral nerves*. Activation of a pure muscle nerve, such as that from the hamstrings, dramatically inhibited the extensor rigidity in the opposed quadriceps muscle. Relaxation of the neck muscles follows stimulation of any branch of the *vth* nerve. When a sensory nerve of the hind- or forelimb is stimulated, the reflex figure described in the last chapter (cf. fig. 39) becomes evident; hence the intersegmental reflexes and reflex patterns laid down in the spinal cord are readily demonstrable in the decerebrate preparation. Inhibition, however, may be sharply localized; touching or pinching the sexual skin, for example, causes the tail to relax, and rubbing facial skin inhibits spasm of the neck muscle (cf. Sherrington, 1917). These reflex responses, predictable and readily evoked in the unanesthetized decerebrate preparation, gave an unparalleled opportunity for systematic study of the reflex activities of the central nervous system. In the hands of Sherrington the decerebrate preparation led to the elucidation of the basic principles of reflex action and integration, his work being ably supplemented in the sphere of postural reflexes by Rudolph Magnus (ch. x).

THE PROPRIOCEPTIVE SYSTEM

The proprioceptors are those end organs which are stimulated by movements of the body itself (ch. i), and it now becomes necessary to examine the action of the proprioceptors in some detail. The proprio-

ceptive system has three primary fibre groups: sensory fibres arising (i) in muscle, (ii) in the labyrinths and (iii) from certain end organs in the viscera. In the present chapter the first group will be considered. The series of observations which led to the recognition of the proprioceptive system in muscle are best presented in historical sequence.

DORSAL ROOT "ATAXIA." Kühne had described the muscle spindle in 1863, and these and other endings were more minutely examined by Ruffini in 1892 (ch. I). Sherrington in 1894 proved these elaborate endings in muscle to be sensory in nature, and he was the first to study their function. It had long been known that cutaneous anesthesia of an extremity does not seriously interfere with its volitional movements, but Magendie's celebrated experiments (ch. II) made it evident that section of the dorsal roots, though altering motility, does not destroy it. The differing effects on motility of cutaneous denervation and of dorsal root section had not attracted attention, however, until Sherrington's studies on the effects of dorsal root section had been made known. Meanwhile clinical observers had described the locomotor ataxia (Romberg, 1851) of tabes, and later pointed out that the primary lesion is in the dorsal roots and dorsal columns of the spinal cord. Evidently, therefore, some relation must exist between the proprioceptors of muscle and the gross ataxia of movement seen by Charcot and others in the late stages of locomotor ataxia. The actual correlation, however, was not made until early in this century.

The first to study the consequences of dorsal root section in monkeys were Mott and Sherrington in 1895; they showed that if one dorsal root to a limb is severed no disturbances of movement can be detected. However, when the whole series of sensory roots supplying the limb was severed, movement, though not abolished, was gravely disturbed. The animal tried to use the limb for feeding, but generally shot wide of its mark and all willed movement exhibited the greatest incoördination. They further pointed out that, whereas the disturbance of motility is slight at the hip, it increases progressively in the more distal joints, amounting in the case of the digits to virtual loss of volitional motility. In this respect it closely simulated the impairment of motility following ablation of the motor region in the cortex. Mott and Sherrington found also that stimulation of the motor cortex gave essentially normal movements in the deafferented extremity, and concluded that sensory data from the active limb were essential for the execution of volitional movement.

A striking experiment which Sherrington demonstrated at a scientific congress early in the century, but evidently never published, related to the difference between motor performance of two cats, one of which had all four extremities cutaneously denervated from knee and elbow distally, and the second cat whose dorsal nerve roots were severed for all four extremities. The first cat was able to walk up an inclined ladder and quietly drink a bowl of milk on the top without even so much as looking at the rungs of the ladder as it proceeded upward. The second cat, whose dorsal roots had been sectioned some months previously, attempted to negotiate the rungs of the ladder, but frequently fell, had always to watch the rungs before taking a step, and actually never succeeded in reaching the top. This demonstrated in a forceful manner that the muscle proprioceptors are essential to orderly locomotion, and that the cutaneous receptors are relatively unimportant.

The reason for such gross disturbances of movement became apparent when the effects of dorsal root section were studied in the decerebrate animal.

LENGTHENING AND SHORTENING REACTIONS. Not only do the isolated extensor muscles of the decerebrate preparation exhibit flexor and extensor reflexes described in chapters VI and VII, but they also show delicate postural adjustments not easily demonstrable in the spinal animal, although clearly present in the decerebrate. These adjustments confer upon the extremity characteristics which are sometimes referred to as "plasticity." These reactions can now be analyzed in terms of the proprioceptive end organs essential for their maintenance. When the quadriceps muscle of a decerebrate cat or dog is fully isolated by appropriate nerve section — leaving the only anatomical structure of the hindlimb still in connection with the cord the quadriceps muscle itself — the muscle exhibits characteristic reactions as follows (fig. 43).

Shortening reaction. If one attempts forcibly to flex the knee when the quadriceps muscle has been isolated in the manner just described, after slight "give" active resistance is encountered. If, however, the knee is passively *extended*, the quadriceps assumes a new position at the shortened length and again immediately exhibits resistance when one attempts to flex the knee. The shortening of the extensor muscle, when its two end points are passively approximated (fig. 43), together with the resistance encountered on subsequently attempting to lengthen it, constitute the shortening reaction (Sherrington, 1909a, 1915).

In attempting to analyze the reflex mechanism and possible receptors involved, the following data are relevant: (i) The shortening reaction occurs in the fully isolated quadriceps muscle debarred from all extrinsic reflex influence arising in skin or antagonistic flexor muscles; this indicates that the reaction depends upon

some intrinsic property of the muscle itself, or upon its nerve supply. (ii) Delicately graded shortening of slight extent (1 mm.), will be followed by a new posture, *i.e.*, the knee remains at the approximate angle of flexion to which it passively carried. (iii) The reaction disappears completely on severing the motor nerve and therefore cannot depend upon any property inherent in the muscle itself. (iv) It disappears correspondingly when the dorsal root supply is severed or when the ventral root supply is cut. (v) It is not affected by removal of the sympathetic innervation. (vi) The shortening reaction grafts itself upon a reflex contraction even more perfectly than upon shortening produced passively. When the shortening

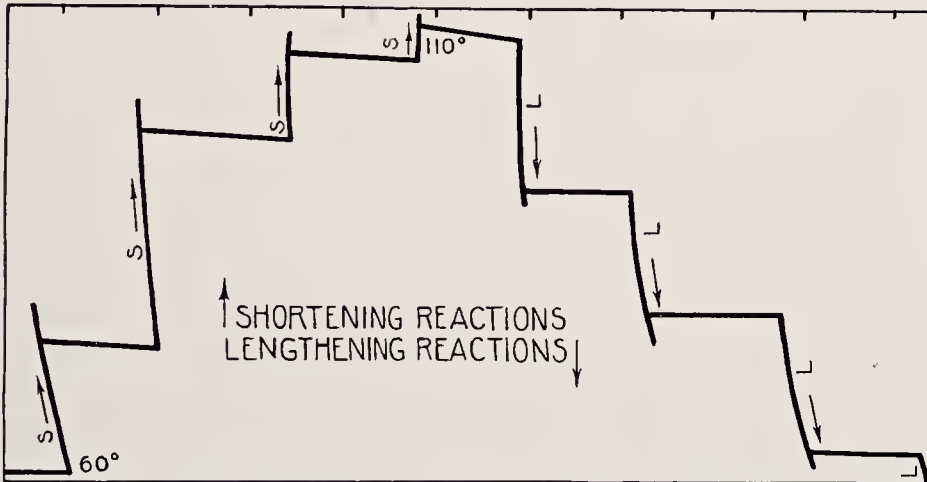


FIG. 43. Shortening and lengthening reactions obtained from isolated quadriceps muscle of decerebrate cat. *s, s, s, s*, indicates "shortening reactions"; *l, l, l, l*, "lengthening reactions"; 60° and 110° mark the angle of knee in respective postures to which limb had been passively carried (Sherrington, *Quart. J. exp. Physiol.*, 1909, 2, p. 118).

reaction was first described, the stretch reflex had not been studied, but it is now obvious that the shortening reaction is a manifestation of the stretch reflex (Fulton, 1926). The stretch reflex has a short latency and any slight tendency toward passive stretch of its receptors is immediately registered, and active contraction thus called forth. For reasons outlined in chapter 1, the stretch afferents have been identified with the muscle spindles, since they are the only end organs in which a distinction is anatomically possible between passive and active tension in muscle, *i.e.*, they lie parallel with the contractile elements.

Lengthening reaction. If, in an isolated extensor preparation similar to that used for demonstrating the shortening reaction, the observer forcefully bends the knee against the resistance offered by the extensor muscles, he will at first encounter considerable resistance, especially if the manoeuvre is carried out rapidly; with increase of the pressure, however, this resistance suddenly "melts" and the knee can then be fully flexed without difficulty (the "clasp-knife" phenomenon). On releasing the limb, the stretch reflex reasserts itself so that the limb remains flexed at

approximately the angle to which it had been carried by this forced manipulation; such lengthening, coupled with the tendency to remain "put," constitute "the lengthening reaction" (fig. 43). This and the shortening reaction together give rise to the property of "plasticity."

The lengthening reaction may be analyzed in a manner similar to the shortening reaction; in this connection the following points deserve mention: (i) It occurs in a fully isolated quadriceps muscle. (ii) It is graded in its intensity, within 1–2 mm. of movement. (iii) It cannot be elicited after the dorsal nerve roots are severed, even when the muscle is executing a crossed extensor reflex. (iv) It disappears under light anesthesia. (v) To palpation the reaction feels like an "inhibitory" relaxation, and indeed similar relaxation can be induced in the quadriceps muscle by stimulating any ipsilateral afferent nerve. An impressive body of indirect evidence has accumulated pointing to the fact that the lengthening reaction *is* a reflex inhibition caused by a particular group of proprioceptive end organs which tend to prevent the development of excessive tension in the muscle. The evidence may be briefly summarized. If the lengthening reaction is a reflex inhibition induced in circumstances which would, if carried further, cause tissue injury, one would expect to encounter other reflex effects similar to those which occur in any nociceptive reaction. In accordance with the principles discussed in chapter VII, an ipsilateral inhibition of an extensor muscle should be accompanied by a crossed extension reaction (Phillipson's reflex); it can be stated categorically *that whenever a lengthening reaction is obtained by forcible flexion a contralateral extensor reflex develops simultaneously*. In Pi-Suñer and Fulton's studies (1928), furthermore, the reflex figure indicating an interaction between fore- and hindlimb reflexes also developed during a lengthening reaction, *i.e.*, ipsilateral forelimb becomes extended, the contralateral forelimb flexed.

Analysis of the lengthening reaction has thus established the existence within extensor muscles of autogenous inhibitors. This system of sensory fibres has not yet been definitely allocated to specific end organs, but there is reason to believe that they belong to the tension recorders, possibly the Golgi tendon organs, which supply the continuous data concerning the state of tension, be it active or passive, within the muscle mass (Fulton and Pi-Suñer, 1928). Some indication of the normal functional activity of these autogenous inhibitors has been obtained through the analysis of the crossed extensor reflex before and after severing the dorsal roots.

Crossed extension reflex of deafferented muscle. Crossed extension reflexes are readily obtained in the muscles of decerebrate animals after they have been deprived of their sensory innervation by appropriate dorsal root section (Sherrington, 1909a). When recorded by an isotonic myograph, it was found that the normal crossed extension reflex continues long after the stimulus has ceased; indeed, the shortening reaction

seems to graft itself for an indefinite period upon the crossed extension reaction. When, on the other hand, the muscle has been deafferented, the tension falls abruptly to the base line and within a few msec. after the end of the stimulus. The difference between the crossed extensor reflex of the normal and the deafferented muscle has also been studied with an isometric myograph, the chief differences being (fig. 44):

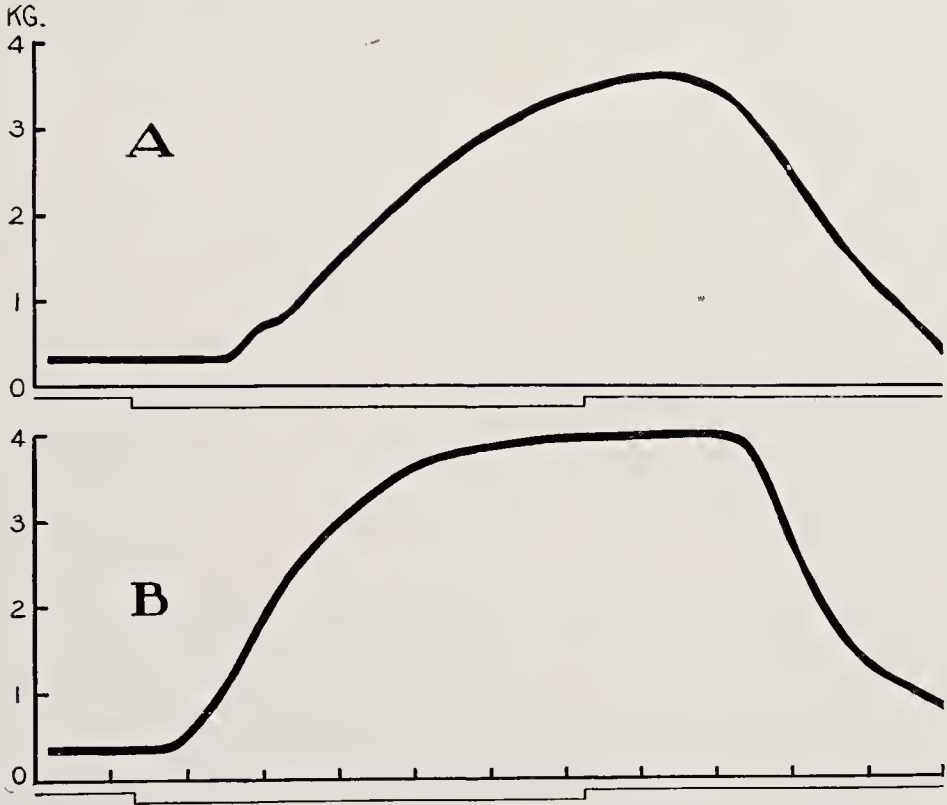


FIG. 44. Crossed extension reflexes of decerebrate cat before and after deafferentation. Rate of stimulation applied to contralateral sciatic nerve 14 per sec. Duration of excitation indicated by short-circuit keys, A, Before dorsal nerve roots were cut. Note greater latency, slower recruitment and slower descent. B, The crossed extension reflex of same muscle two hours after intradural section of dorsal root supply of the muscle; same strength duration and rate of stimulation and same initial tension. Note more abrupt rise of tension and more rapid decline. (Fulton and Liddell, *Proc. roy. Soc.*, 1925, 98B, p. 214.)

(i) The latency of the response is shortened and is more readily obtained, rising more rapidly in deafferented muscle than the normal. (ii) A somewhat higher total tension is reached with stimuli of the same duration and intensity. (iii) The tension falls more rapidly at the end of the contraction. One can thus detect in such a reflex, when afferents are intact,

the operation at the beginning of the reflex, of autogenous inhibitors which prevents too rapid rise of tension and, at the end of the reflex, stretch reactions cause the tension to relax more slowly. In other words, the sensory nerves to muscle make automatic adjustments which lead to greater smoothness of response and prevent abrupt tension changes which might injure the muscle. It is thus clear that "ataxia" resulting

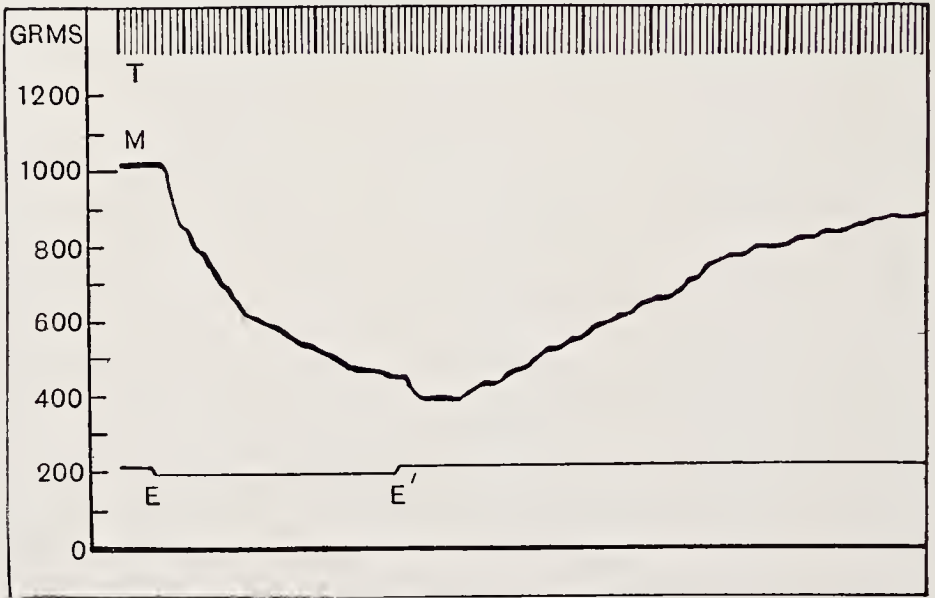


FIG. 45. Effect on stretch reflex of quadriceps muscle of stimulating undifferentiated hamstrings via their anterior nerve roots in decerebrate cat during interval E-E'. Note prompt inhibition; time indicated above in 0.02 sec. (Cooper and Creed, *J. Physiol.*, 1927, 62, p. 207.)

from interruption of sensory fibres from muscles is manifested in reflex as well as in voluntary movement (Fulton and Liddell, 1925a).

Reflex effects of contraction. Cooper and Creed (1927a&b) introduced the ingenious method of stimulating muscles with afferent nerve supply intact through their cut ventral nerve roots, while an opposed muscle is engaged in active contraction. In these circumstances, contraction, *e.g.*, in the hamstrings, evokes proprioceptive impulses which actively inhibit the ipsilateral quadriceps (fig. 45) during either a stretch or a crossed extension reflex. Strychnine does not reverse this inhibitory effect. Similarly, weak contraction of quadriceps evoked by faradizing its cut anterior roots serves, through activation of its proprioceptors, to suppress activity of the fellow quadriceps of the opposite side. These important synergic actions obviously reinforce the central mechanism for

reciprocal innervation, and play a part in regulating reflex stepping and rhythmic reflexes involving successive induction.

DECEREBRATE RIGIDITY IN MAN

Decerebrate rigidity has often been reported in man, sometimes occurring in the form of tonic fits, but more often appearing as an enduring rigidity developing prior to death. Jackson's (1870) "cerebellar" seizures actually represent functional decerebration near the junction between the pons and medulla. Similar functional decerebration was reported by Cushing in 1905, but prior to the work of Magnus and de Kleyn (1912) the criteria of the decerebrate state in man had not been fully recognized. As in animals, the rigidity of the decerebrate state is plastic in character, *i.e.*, accompanied by lengthening and shortening reactions, and the tonic reflexes described by Magnus and de Kleyn (ch. x) are also demonstrable. A miscellaneous group of premortem rigidities, some of them representing decerebrate rigidity, were reported in 1920 by Kinnier Wilson; several were accompanied by tonic fits; but the neck and labyrinthine reflexes were not studied. The cases generally designated "decerebrate rigidity" in man, such as those of Walshe (1923a&b, 1925) and Davis (1925), which are actually "decorticate rigidities," may be briefly described.

CASE 2. Suprasellar cyst in human being causing quadriplegia and later, signs of decortication: lengthening and shortening reactions and tonic neck reflexes (Walshe, 1923b).

A woman of 23 years was found to have a suprasellar cyst. Her history was briefly as follows: One year before coming under observation she had begun to have headaches which were followed by a sudden loss of vision and signs of intracranial pressure. Following a palliative operation (decompression), she developed a hemiplegia on the opposite side and later became semicomatose. Gradually a condition of quadriplegia developed and the following features of her condition indicated that her lesion had caused functional decerebration. When lying supine, her arms were held across the body semiflexed at the elbows with forearms slightly pronated and wrists and fingers flexed. The legs were held in strong extension with slight adduction and the feet in plantar flexion. Lengthening and shortening reactions could be obtained by passive manipulation of the lower extremities, *i.e.*, there was a typical "clasp-knife" phenomenon with vigorous resistance at first to flexion and then the extensor muscles would suddenly give way (lengthening reaction) and within certain limits the limbs would remain in any position in which they were passively placed. Tendon reflexes were brisk and the muscles showed a tendency to remain in a more shortened state after a series of tendon reflexes. Plantar stimulation evoked a vigorous flexor reflex. The neck and labyrinthine reflexes of Magnus and de Kleyn were well developed, rotation of the chin to the right causing in-

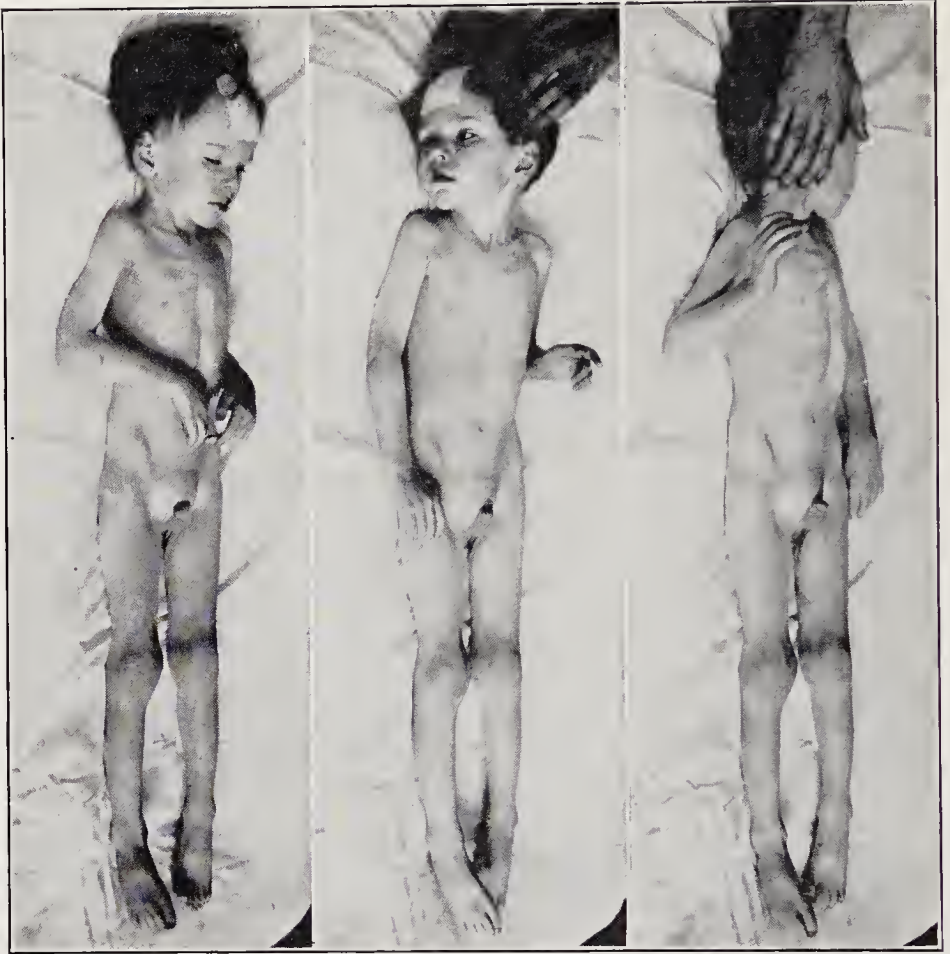


FIG. 46. The Magnus and de Kleyn reflexes induced by rotation of the head in a decorticate human being — *i.e.*, a “high” decerebration (see chapter x; from Davis, L. E. *Arch. Neurol. Psychiat.*, 1925, 13, 569–579).

creased extension of the right lower extremity and marked extension with inward pronation of the upper extremity (ch. x).

CASE 3. *Suprasellar cyst in child causing gradual “decerebration” with appearance of Magnus and de Kleyn reflexes and plastic hypertonicity.*

The present case was reported from Cushing’s clinic by Davis (1925) and is illustrated in figure 46. It related to a child of 4 years who had a suprasellar cyst with marked calcification. At the age of $2\frac{1}{2}$ years he had become blind and in June 1923 began to have headaches and vomiting. In December 1923 he was stuporous and was brought to the hospital in that condition. Examination showed complete quadriplegia and marked extensor rigidity. The child was under observation until his death March 12, 1924. During the last two months of the child’s illness, he exhibited the characteristic decorticate posture with marked tonic neck reflexes and lengthening and shortening reactions.

From these cases it is manifest that the lower extremities in the "decerebrate" state exhibit an attitude of strong extension with slight inward rotation and flexion of the toes. The attitude assumed by the upper extremities has been a source of considerable dispute, largely because clinical observers interested in the subject have been unaware of the differences between a "high" and "low" decerebration in primate forms. The facts are these: Bilateral decortication in a macaque (or mere removal of both frontal lobes) causes the upper extremities to assume a strongly semiflexed hemiplegic posture in which the reflexes of Magnus and de Kleyn are readily demonstrated (Bieber and Fulton, 1938). The extremities, furthermore, exhibit moderate spastic rigidity (chapters x and xxi). When, however, a primate is decerebrated at the midcollicular level of Sherrington, thus excluding hypothalamus and red nucleus levels, a much more intense spastic rigidity develops, *and the upper extremities are thrust backwards in rigid extension with pronation* (Sherrington, 1898, p. 320), assuming the "typical decerebrate attitude" of Kinnier Wilson (1920). In these circumstances the rigidity is likely to be so intense that the Magnus and de Kleyn reflexes become difficult to bring out (see Penfield and Erickson, 1941).

OTHER FUNCTIONS OF MEDULLA OBLONGATA

It is beyond the scope of the present monograph to deal at length with the cranial nerves. If, however, one glances at a diagram of the medulla oblongata one finds in its posterior half the nuclei of the ixth, xth, xith and xiith cranial nerves. Each one of these nuclei is sausage-shaped and traverses nearly a third of the length of the floor of the medulla. In the middle part of the medulla, and extending laterally into the upper regions of the walls of the ivth ventricle, are the vestibular nuclei, made up of four fairly discrete nuclear masses: the *lateral* (Deiters, origin of vestibulospinal pathway), the *superior* (Bechterew), the *medial* (Schwalbe) and the *spinal*. The nuclei of the viith and viiith nerves lying in the brain stem just rostral to the medulla are, strictly speaking, in the metencephalon, along with the superior part of the vestibular nucleus of Bechterew. The functions mediated by these and other nuclear masses in the medulla can to some extent be inferred from the well recognized functions subserved by the cranial nerves to which the medulla gives rise.

DEGLUTITION AND VOMITING. Miller and Sherrington (1916) have stud-

ied the bucco-pharyngeal stage of reflex deglutition in the decerebrate cat, finding that moderate pressure applied to an area 2.5 cm. in length on the back wall of the pharynx regularly evoked swallowing. Occasionally the swallow could be elicited by similar pressure to the soft palate, epiglottis and posterior part of the dorsum of the tongue. A drop of water applied to the same region of the tongue also incited swallowing. On testing various foods and chemical agents, the most effective excitant of reflex swallowing was diluted ethyl alcohol. Castor oil, on the other hand, had virtually no influence upon the reflex; if, however, ethyl alcohol were mixed with castor oil, it was swallowed with avidity—a point for pediatricians to remember.

Certain noxious agents also initiated the reflex, but after one or two swallows, the same agent evoked retching and even vomiting. It proved difficult to bring about the swallowing of solid foods. Sensory stimulation of any branch of the trigeminal nerve, especially the lingual, inhibited reflex swallowing. On turning to the floor of the 14th ventricle itself, weak faradization with a monopolar electrode of a region corresponding with the middle of the xth nerve nucleus, evoked the swallowing and simultaneously arrested respiratory movements. From this centre the phenomena of facilitation, summation and refractory period were all demonstrable.

The vomiting reflex of the decerebrate cat has been less fully studied and deserves more careful analysis. Vomiting movements were recorded by Miller and Sherrington, but the character of the stimulus essential for the production of vomiting, the precise route of the afferent pathways of the reflex (presumably vagus) have not been determined (see also Miller, 1924; ch. vi). Reflex vomiting can readily be evoked by stimulating the lateral part of the floor of the 14th ventricle, and vomiting is frequently induced in human beings under local anesthesia by mere manipulation of the medulla.

RESPIRATORY CENTRE. Although subject to regulation both from the hypothalamic and cortical levels, rhythmic respiratory movements are maintained by the medulla oblongata from foci which, thanks to the studies of Le Gallois (1812), Scott and Roberts (1923), Ff. Roberts (1925), and Lumsden (1923), were well recognized, but until recently were not clearly defined anatomically. The most notable recent development in the physiology of the medulla oblongata, especially of its large and ill-defined reticular formation, has been the positive localization of the sev-

eral respiratory centres by Pitts, Magoun and Ranson(1939a), coupled with their analysis of the interrelation of these centres(1939b) and their descending pathways(Pitts, 1940, 1941, 1942b). Using Horsley-Clarke stimulation, they have found a well-defined *inspiratory* area lying in the ventral reticular formation of the cat's medulla oblongata lying immedi-

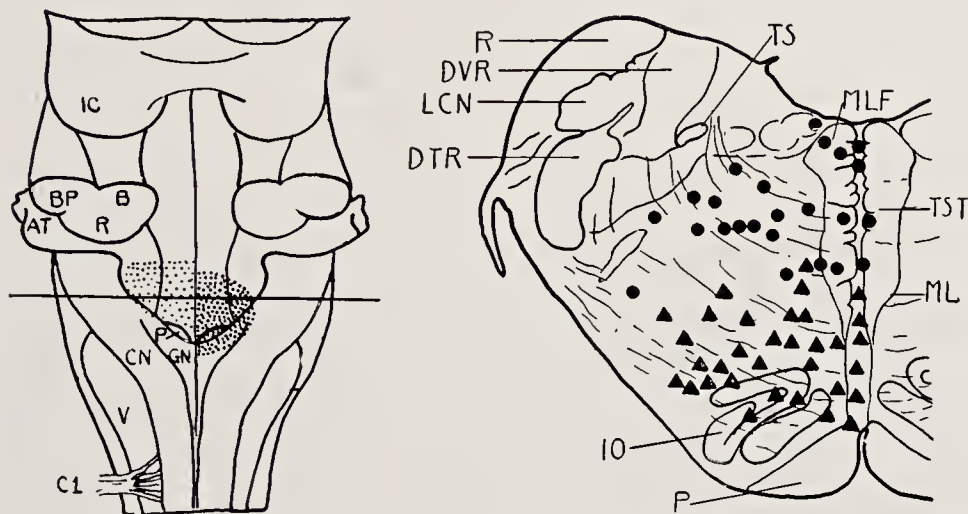


FIG. 47. Left. Inspiratory and expiratory centers of cat, after Pitts. On right dotted area responsible for *inspiration* lies ventral to dotted area on left which controls *expiratory* movements.

Right. An enlarged cross section of the medulla at the level indicated by horizontal line in left diagram. Circles indicate expiratory points; triangles inspiratory foci.(From Pitts, Magoun and Ranson, *Amer. J. Physiol.*, 1939, 126, p. 678.)

AT, acoustic tubercle
B, brachium conjunctivum
BP, brachium pontis
C1, first cervical segment
CN, cuneate nucleus
DTR, descending trigeminal root
DVR, descending vestibular root
GN, gracile nucleus
IC, inferior colliculus

IO, inferior olivary nucleus
LCN, lateral cuneate nucleus
ML, medial lemniscus
MLF, medial longitudinal fasciculus
P, pyramid
R, restiform body
TS, tractus solitarius
TST, tectospinal tract
V, tuberculum cinereum

ately over the inferior olive(fig. 47, right). When this region is stimulated electrically, the chest and diaphragm remain in fixed maximal inspiration, rhythmic breathing is abolished, and death may occur if the stimulation is continued.

An *expiratory* area was similarly delimited lying "dorsal to, slightly cephalic to, and cupped over the cephalic end of the inspiratory reticular formation"(fig. 47). The expiratory movement evoked by stimulating

this area is somewhat less intense than the inspiration evoked from the inspiratory area, but it involves both thorax and diaphragm and in some instances is maximal. If stimulation persists, a maximal expiratory posture may be maintained for two to three minutes, but death does not supervene, since inspiration gradually breaks through. The respiratory movements observed in these studies were well integrated respiratory acts involving simultaneously thoracic and diaphragmatic musculature and hence cannot be due to stimulation of efferent or afferent fibre tracts, but rather to a focus of neuronal integration. Reactions were independent of the anesthetics used, and they could also be obtained in unanesthetized animals having surgically implanted electrodes. Caudal to these foci, expiratory and inspiratory hyperactivity could be obtained in the presence of superimposed rhythmic respiration. The latter effects were interpreted as due to stimulation of descending tracts. In passing one should note that the precise localization of the inspiratory and expiratory centres coincides with the general localization of the corresponding centre in man given by Finley(1931) in his two cases of primary respiratory failure from the medullary lesions.

Respiration is also influenced from *supramedullary* levels. Thus, Magoun(1938) finds that the well known inhibitory effect on respiratory movements resulting from hypothalamic stimulation is considerably depressed when the hypothalamus is stimulated some weeks after removal of the cerebral cortex. This suggests that the normal response is due to activation of corticofugal fibres which pass from the cortex through the hypothalamic area(see also Pitts, 1940, 1941; ch. XXI).

Regulation of respiration. The regulation of respiratory movements is a problem of general physiology in the broadest sense and general texts should be consulted. The neurological pathways and mechanisms have, however, been notably elucidated by the more recent work of Pitts(1942a&b). Thus, low intensity or low frequency faradic stimulation of the *inspiratory* centre produce the same effects on phrenic neuron discharge as normal activation of the respiratory centre by the blood stream, *i.e.*, increased frequency of discharge, increased duration of activity and recruitment of inactive motor units. Stimulation of the *expiratory* centre, on the other hand, produces exactly the reverse effect, *i.e.*, decreased frequency of discharge, decreased duration of activity and reduction of numbers of active neurons. Varying the intensity of stimulus or its frequency gives indication that each phrenic neuron receives excitation from the inspiratory centre through a number of separate pathways. The average level of excitation of the neuron is dependent upon the number of these pathways and their frequency of transmission. The rate of discharge indicates the level of excitation. All neurons of the phrenic motor neuron pool receive some excitation from the inspiratory centre, but much of this stimu-

lation is of subliminal intensity. Any increase in activity of the neurons of the inspiratory centre increase the frequency of discharge of phrenic neurons and it may also recruit additional phrenic units. Thus the neurons of the inspiratory centre and of expiratory centre are closely interconnected through an inter-neuron system. Pitt's analysis of single phrenic units adds one more to the distinguished series of contributions which have come in recent years through functional isolation of individual neuronal elements. In his second paper Pitts(1942b) finds that the central respiratory system can be functionally divided into four subsidiary systems: (i) respiratory-centre motor neuron system; (ii) vagal inhibitory system; (iii) brain stem inhibitory system; (iv) other excitatory and inhibitory systems. The respiratory-centre neuron system regulates depth of inspiration by controlling motor units impulse frequency and the number of units activated. The discharge of this system when isolated is continuous, and regulated in degree by the carbon dioxide tension of the arterial blood. The vagal inhibitory and brain stem inhibitory systems serve in a parallel manner to inhibit periodically the activities of the respiratory motor neuron system. Such periodic inhibition leads to rhythmic respiration and provides the ground work for variation in rates.

Another study on the medulla is that of Wang(1938), who finds that local application of pituitrin, pitressin, histamine and acetylcholine to the floor of the fourth ventricle in cats under pentobarbitol anesthesia causes a small depressor response. With acetylcholine, however, there may also occur a delayed pressor response following initial depression.

CARDIOVASCULAR REFLEXES. Many reflexes affecting the cardiovascular system are integrated at the medullary level(Ranson and Billingsley, 1916). Thus, all those reactions essential for maintenance of the blood pressure, vasopressor reflexes, vasodilator reflexes, reflexes of the carotid sinus, and the various cardiac reflexes, including the Bainbridge reaction, all depend upon the integrity of the medulla oblongata. As with respiration, however, the functions which these reflexes subserve are subject to higher integration from hypothalamus, striatum and cortex(ch. XXIII).

SUMMARY

Sherrington found in 1898 that prepontine transection of the brain stem induced a state of exaggerated posture characterized by continuous spasm of the skeletal muscles, predominantly the extensors. The phenomenon was termed "decerebrate rigidity," and he interpreted it as a "release phenomenon" due to interruption of projections from higher levels. The projections in question could not be the pyramidal pathways, since mere removal of the cerebral hemisphere failed *in cat and monkey* to cause the rigidity. When severed at the intercollicular level, the rigidity came on at once. *If only half the brain stem were severed, the rigidity was homolateral.* Hence, decerebrate rigidity must

depend upon interruption of some extrapyramidal pathways which have already decussated at this level.

The integrity of the vestibular nuclei is essential for the continuance of decerebrate rigidity. This suggests that rigidity is primarily due to the release of the vestibular nuclei from higher extrapyramidal control. Early studies of Weed(1914) and unpublished work of Keller, however, indicate that section at the caudal tip of the pons also may cause flaccidity.

The rigidity developing after intercollicular section in primates, as well as in dogs and cats, is characterized by an extensor posture of the lower *as well as of the upper extremities*. Tonic neck and labyrinthine reflexes can be demonstrated, but in primates these reactions are most readily brought out following "decerebrations" at higher levels. In these higher decerebrations the upper extremities assume a flexed posture, which is also true of forward decerebrations in man.

Extensor muscles in decerebrate rigidity exhibit the lengthening and shortening reactions. The lengthening reaction is brought about by reflex inhibition and is accompanied, in the hindlimbs, by crossed extensor reactions, and other postural changes in the forelimbs. The shortening reaction is a manifestation of the stretch reflex. Together they give rise to the property of plasticity. They are both dependent upon the integrity of the dorsal nerve roots.

Other reflex functions mediated by the medulla oblongata are: swallowing, vomiting, respiratory movements, and a large group of cardiovascular reflexes, which serve to maintain the blood pressure at a constant level.

X

THE MEDULLA OBLONGATA AND MIDBRAIN: POSTURAL REFLEXES

HISTORICAL NOTE

In 1924 there appeared from the press of Julius Springer a remarkable book by the late Rudolph Magnus bearing the brief title *Körperstellung* — literally “body posture.” Like Sherrington’s *Integrative action of the nervous system*, this book became almost immediately it was issued one of the cornerstones of modern Neurology, ranking with other landmarks of the subject, such as those of Willis (1664), Whytt (1751), Magendie (1822), Hitzig (1874) and Ferrier (1876). Magnus’ investigations had their beginnings in Sherrington’s Laboratory at Liverpool in 1908 with his paper published from there on the regulation of movement (1909). His later work was carried on with a series of collaborators including A. de Kleyn who joined him early, and later J. G. Dusser de Barenne, G. G. J. Rademaker, R. Schoen, O. Girndt, E. A. Blake-Pritchard and Georg Schaltenbrand. Sherrington had been using the decerebrate preparation to study individual reflexes and the underlying mechanism of reflex transmission within the nervous system. After Magnus had left Liverpool, Sherrington and Magnus independently noted the effects of rotation of the head on the posture of a decerebrate cat. When Sherrington learned that Magnus had seen the reaction, he urged him to pursue it, and stated that the observation would be his to elucidate.* Magnus quickly appreciated its importance and devoted most of his time during the remaining years of his life to its analysis. He died a year after delivering his Cameron Prize Lectures on the physiology of posture at Edinburgh, May 19th, and 20th, 1926 (see Magnus, 1926). The outline of presentation in the present chapter is based upon this lucid

* In their first paper on the effects of head rotation by Magnus and de Kleyn (1912, p. 468) the following reference is made to the independent discovery: “While this research was in progress, one of us (M.) learned through the kindness of Prof. Sherrington that he had likewise found in the decerebrate cats on turning the head a wane of tonus in the hind (less in the fore) ‘skull limb.’ [See Sherrington, C. S., 1910]. Professor Sherrington was gracious enough to send us his protocol for our judgment. In his experiments also the reaction, after section of both viii th nerves or destruction of both labyrinths, remained, as when both trigemini were also cut. On the other hand, the reaction was abolished by section of both the first [viii th nerves] and the dorsal roots of the three pairs of cervical nerves. The disclosure and origin of head-turning reflexes through independent experiments of two different Laboratories are thus firmly established.” Sherrington (1910, p. 112) states: “Again active or passive rotation of neck on its long axis in the decerebrate preparation inhibits extensor tonus in hind-limb on the side of the lowered pinna and causes active flexion of knee; and does so after severance of both cranial vi ths and both *octavi*. Again, in the deafferented vastocurreus (decerebrate preparation) though the steady enduring tonus ensuing on decerebration is characteristically absent from the muscle, nevertheless from time to time for relatively short periods tonic contraction of it occurs traceable to afferent sources altogether headward of hind-limb.”

summary of his work. For details concerning the early history of work on the labyrinth attention is directed to the full summary and excellent bibliography by Dusser de Barenne(1934).

IN the last chapter the "high" and the "low" decerebrate preparations were contrasted—a distinction which is of importance in all mammals. The principle difference between the two is that animals with high decerebration have righting reflexes, whereas the low decerebrate, or "oblongata" animal, lacks these reactions. A source of confusion in the literature of the subject lies in the fact that the midbrain, or thalamic animal of Magnus, exhibits a reflex status that varies widely among different species. Thus, the midbrain dog or cat (with part of the thalamus intact and hence often designated a thalamic animal) has, when on its four feet (see Bard and Rioch, 1937), normal distribution of postural tone, and is capable of walking, whereas the thalamic monkey has abnormal posture and is quite unable to walk. For this reason the reflex status of the thalamic monkey is frequently confused with that of the oblongata dog or cat, which also has abnormal posture, *i.e.*, "decerebrate rigidity," and is similarly unable to walk. As Magnus gave only limited attention to postural reflexes of primate forms, the following account will be supplemented with such information as is now available from monkeys and chimpanzees.

The postural reflexes are divided into three categories: (i) *local static reactions* in which only one part of the body, such as a limb, is involved: (ii) *segmental static reactions* which affect whole segments of the body (*i.e.*, both sides), such as the hindlimbs, the forelimbs and neck muscles, etc., and (iii) *general static reactions* in which various segments are involved which correspond to the intersegmental reactions of the spinal animal. These reactions will be discussed under two principal headings: (i) the oblongata animal and (ii) the midbrain or thalamic animal.

OBLONGATA OR "LOW" DECEREBRATE ANIMAL

LOCAL STATIC REACTIONS. Magnus poses the problem of the local static reaction in the following terms: "A movable limb is at times used as an *instrument* for very different purposes (such as scraping, scratching, fighting, etc.), and moves freely in all joints, whereas at other times it is transformed into a stiff and strong *pillar*, which gives the impression of being one solid column, able to carry the weight of the body. Experiments have shown that this is accomplished by a series of local static

reflexes." To become pillar-like the joints of a lengthy extremity must become fixed, and fixation of joints involves the operation of tendons and fascia and also the *simultaneous contraction of opposing muscle groups* (Beevor, 1904). The stretch reflex discussed in chapter VII plays an important part in these local static reactions, but its action is accompanied by reciprocal inhibition of the flexors. The stretch reflex would, therefore, be incapable of giving an entire limb a rigidly fixed posture; Magnus and his students accordingly sought some other adjuvant reflex. The missing reaction was soon found in a quite unexpected manner in a chronic decerebellate dog. If such an animal is in a supine position with head flexed slightly forward, gentle contact with the pads of the foot evokes enduring extension of the whole limb. The stimulus required is so delicate that one gains the impression that the foot is being drawn after the receding finger by a magnetic force. For this reason the reflex was at first designated "the magnet reaction." It disappears as soon as the finger is withdrawn. This phase of the response is purely cutaneous in origin, and therefore *exteroceptive*; slight separation of the pads of the foot, however, also evokes an entirely similar reaction after the skin has been anesthetized. Such separation stretches the small muscles of the foot and is therefore *proprioceptive* in origin. Normally both varieties of stimulus are in operation, since a dog's toe pads would be separated by its own weight, and in addition cutaneous stimulation would arise from contact with the ground. Although first observed in the decerebellate preparation (cf. ch. xxv), these responses, which were designated "the supporting reaction," are also found (poorly developed) in chronic oblongata and in midbrain animals (Schoen, 1926) and in man (Schwab, 1927).

Positive supporting reaction. The reflex transition from a toneless, flexible limb to the "stiffness of a rigid pillar" is designated the positive supporting reaction; the relaxation of such a rigid limb, after withdrawal of the stimulus, is called the negative supporting reaction. The positive phase of this reflex is present, though poorly developed, in the oblongata animal, and is best studied in the decerebellate dog where it comes on some hours after the procedure, and continues to increase in intensity for several days; it is more conspicuous in dog than in cat. It is probably present in monkey, since it can be demonstrated in the decerebellate monkey, but has not yet been adequately studied in the oblongata preparation. Rademaker has insisted that the supporting reactions are in fact

seriously disturbed by removal of the cerebral cortex, but Bard and Rioch (1937) have proved that they are present in the decorticate animal; the extensor thrust discussed in chapter VIII is the spinal manifestation of the positive supporting reaction.

Negative supporting reaction. Active inhibition of the muscles involved in the strong extensor posture of the supporting reaction is in itself a well defined proprioceptive reflex. Flexion of the digits and the hand in the forelimb and plantar flexion of the toes of the hindlimb is the effective stimulus. Stretching of the small muscles of feet and hands evokes reflexes in muscles of the proximal joints, while relaxation of the smaller muscles inhibits that contraction. As a consequence of the inhibition, the whole limb, including the shoulder, becomes "loosened" and free for movement.

SEGMENTAL STATIC REACTIONS. Segmental static reactions refer in part to reflex patterns already discussed in earlier chapters, notably the crossed extension reflex which, in combination with positive supporting reaction, serves to maintain the animal's weight. Another segmental static reaction is the oblongata component of the hopping reaction (see below) which Magnus called "Schunkel-reflex" — the shifting reaction. If, for example, the right hindlimb is passively flexed by an observer and the body then allowed to veer towards the right side, strong extensor posture immediately develops in the flexed limb so that it is prepared to support the weight of the body. This reflex is due to stretch of the adductor muscles of the left limb. Similar responses can be detected in the forelimbs both when veering laterally and when veering fore and aft. These reactions are evidently due to stretching of specific groups of muscles. Although present in the chronic oblongata animal, this reflex is better developed in the midbrain preparation. According to Bard (1933), the reaction is present in the monkey after removal of the frontal lobes, and hence it is no doubt present in the midbrain animal, and possibly in the oblongata monkey. "These and other segmental static reactions, in which stimulus and effect are not confined to the same limb, but to the same segment, show the interconnections of separate parts of the body in static function" (Magnus, 1926).

GENERAL STATIC REACTIONS. General static reactions constitute the larger and more important fraction of static reactions. The fundamental condition for every static reaction — local, segmental or general — is that the animal be able to stand. A question at once arises as to what

parts of the nervous system must be present to ensure standing. The spinal animal, although it has poorly developed stretch reflexes and fragmentary static reflexes in the form of the extensor thrust, can not stand. The oblongata preparation, on the other hand, exhibits an exaggerated form of reflex standing and when placed on all four feet is well able to maintain the weight of the body; but it can easily be pushed over because of the absence of hopping and other reflex adjustments. The most important of the general static reactions of the decerebrate animal are those governed by the neck muscles and the labyrinths. The circumstances leading to the discovery of these reactions may be given in Magnus' own words:

"General static reactions in the decerebrate animal can most easily be induced by changing the position of the head. This was discovered by chance. Many years ago I prepared a decerebrate cat with cross section of the low thoracic cord, in order to study some reflex reactions of the tail muscles. For this purpose I brought the animal from the lateral into the supine position and noticed to my surprise a slow but very strong 'pathetic' extension of the fore-limbs, which disappeared when the animal was again placed upon its side. Other changes of position evoked also tonic reactions of the fore-limbs. Subsequent repetitions of the same experiment showed that various animals reacted differently. A long experimental analysis, in which I was joined by my friend and collaborator, de Kleyn, was necessary until we understood the phenomenon completely. As usual the result was comparatively simple. It is possible, by giving to the head different positions, to change the distribution of tone in the whole body musculature, and, as far as decerebrate preparations are concerned, especially in the above-named group of antigravity muscles. The most striking reactions appear in the extensors of the limbs and in the neck muscles. The effects observed are the result of combined reflexes from the labyrinths and from proprioceptive neck receptors, and as the relative strength of these two influences varies from animal to animal, the different results of subsequent experiments can be understood. In this way it is possible to impress upon the whole body different adapted attitudes by changing only the position of the head. These reflexes therefore may be called *attitudinal reflexes*."

Changes of position of the head in relation to the body stimulate the neck muscles, whereas change of position of the head in space excites the labyrinth. The two sets of reflexes will be discussed separately.

TONIC NECK REFLEXES. In order to study the influence of the neck muscles upon distribution of tone it is necessary to destroy both labyrinths. In a long series of investigations with de Kleyn, Magnus made the following striking disclosures: (i) Rotation of the jaw to the right causes prompt increase in extensor contraction of the right limb ("jaw limb"), and relaxation of the left limb towards which the vertex is rotated ("skull limb"; figures 45 and 46). (ii) Deviation of the head

towards one shoulder similarly causes extension in the fore- and hind- "jaw" limbs and relaxation of the "skull" limbs. (iii) Dorsiflexion of the head in all mammals, save the rabbit, causes extension of the forelimbs and relaxation of the hindlimbs — the attitude assumed by a cat looking upward towards a shelf. (iv) Ventroflexion of the head causes flexion of the forelimbs and extension of the hindlimbs — the attitude of an animal looking under a piece of furniture. The rabbit, which is the exception to the rule, exhibits extension of all four limbs on dorsiflexion of the head, and flexion of all four limbs on ventroflexion. (v) A special reflex, known as the *vertebra prominens reaction*, consists of applying mechanical pressure to the lower part of the cervical vertebral column which results in uniform relaxation of all four limbs. With the possible exception of the last reflex, the afferent nerves involved pass through the three uppermost dorsal nerve roots of the cervical region. The actual centres in the spinal cord are found in the first or second cervical segment.

These reactions exhibit obvious purpose: Thus, when a cat standing on all fours hears a noise ahead and to its right, its head turns and the extremities on the right side automatically exhibit increased extensor posture, which would tend to support the weight of the body in case the animal takes off with its left forelimb. If the noise is made by a mouse, the cat has only to decide whether to dash at it or not — the postural adjustments suitable for the act are made automatically.

The tonic neck reflexes were also studied by Magnus (1918, 1922) in decerebrate and in decorticate monkeys, and recently by Dow and Fulton (1938) in labyrinthectomized monkeys exhibiting the thalamic reflex status which follows bilateral removal of the motor and premotor areas of the frontal lobes (ch. XXI). The general reactions are similar to those of cats and dogs. Thus, as illustrated in figure 45, rotation of the chin to the right causes vigorous extension of the right upper and lower extremities; the "skull" extremities, on the other hand, become flexed, and in these circumstances the digits, both of the upper and lower extremities, exhibit the *grasp reflex* (ch. XXI). The grasp reflex thus becomes a part of the postural reflex mechanism affected by the tonic neck reflexes (Bieber and Fulton, 1938; Fulton and Dow, 1938). Ventroflexion of the head causes flexion of the upper extremities with extension of the lower, and along with this there is accentuation of the grasp reflex in the upper extremities and inhibition of the grasp reflex in the lower. Dorsiflexion

of the head causes (i) extension of the upper extremities with inhibition of their grasp reflex, and (ii) flexion of the lower extremities and accentuation of the grasp.

TONIC LABYRINTHINE REFLEXES. By section of the dorsal roots of the upper three cervical levels the tonic neck reflexes are excluded and the operation of the labyrinthine reflexes can then be examined. The same objective can be attained by immobilizing the head in a plaster cast so that it can not move in relation to the body. As such a preparation is brought into different positions in space, marked changes occur in the resting posture of the oblongata animal. Maximal extension is seen in the supine position with the snout about 45° above the horizontal plane. The minimal labyrinthine position is in the prone posture with the snout tilted 45° below the horizontal plane. The minimum and maximum, therefore, differ by 180° . In all other positions, the distribution of extensor tone is intermediate between these two extremes. It should be emphasized that these reflexes are not elicited by movement *per se*, but depend solely upon position in space, *i.e.*, they are quite independent of angular acceleration. That they have their origin in the labyrinth follows from the fact that they disappear completely after bilateral labyrinthectomy. A labyrinthectomized decerebrate cat with upper cervical roots cut exhibits rigidity of its extensor muscles, but there are no changes induced by alteration of position in space. The structures of the labyrinth which give origin to the static reactions are the otolith organs.

Proof of the otolithic origin of the tonic labyrinthine reflexes was a matter of considerable difficulty, since it is impossible to carry out an isolated extirpation of the otolithic maculae without disturbing the semicircular canals (fig. 48). It was possible, however, to destroy the otolith in guinea pigs by centrifuging them at a fairly high speed. The otolithic membranes were detached by this procedure without disturbing the semicircular canals. In such animals the tonic labyrinthine reflexes were completely destroyed and on serial section their semicircular canals proved to be still intact. Reactions arising from angular or rectilinear acceleration in space (semicircular canals) were still present. Magnus makes the further point that in a maximal extensor position the otoliths pull on the utricular maculae rather than press on the macular epithelium as some had inferred.

The labyrinth also affects the neck muscles by causing them to execute movements which may be synergic with the movements which would be evoked from the labyrinth alone, or antagonistic. The connection, therefore, of the labyrinth with the limb may be regarded as double: (i) by tonic labyrinthine reflexes affecting the limbs directly, and

(ii)indirectly by labyrinthine reflexes which affect tonic neck reactions. This means that when the tonic labyrinthine and neck reflexes are both present they support one another and are to be regarded as complementary tonic reactions. In certain circumstances the influence from the two

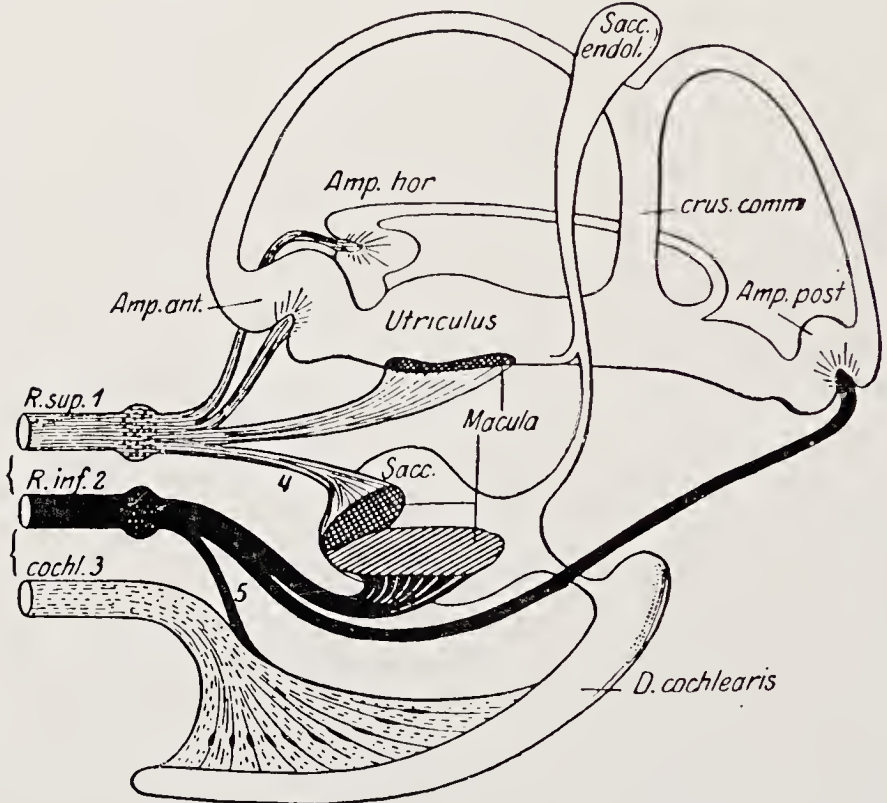


FIG. 48. Innervation and general relations of membranous labyrinth after de Burlet. *R sup. 1*, proximal root of eighth nerve. *R inf. 2*, a part of distal root of eighth nerve (another part of which forms cochlear nerve). The two swellings on the *R sup. 1*, and *R inf. 2*, together constitute Scarpa's ganglion (de Burlet, *Anat. Anz.*, 1924, 58, 26-32).

sources may be opposed in effect, which results in an algebraical summation of effect. An example of such interaction cited by Magnus (1926) is as follows:

"This coöperation gives rise to very characteristic attitudinal reactions of decerebrate animals. Place a cat in the prone position upon the table and flex the head ventrally, then the labyrinths come into the minimum position, and all four limbs will tend to relax. The neck influences cause relaxation of the fore-limbs and extension of the hind-limbs. Both groups of reflexes, therefore, coöperate in the fore-limbs, which show distinct relaxation, whereas the hind-limbs may not change at all, because the influences from neck and labyrinths act in opposite

senses. If with the prone position of the animal the head is bent dorsally the resulting removal of the labyrinths from the minimal position causes extension of all four limbs. The neck reflexes evoke extension of the fore-limbs and relaxation of the hind-limbs. The combined effect is strong extension of the fore-limbs and only slight changes in the hind-limbs. Head movements, therefore, in a ventral and dorsal direction have a very strong influence on the fore-limbs, whereas the reaction of the hind-limbs is much weaker."

Corresponding reactions occur following section of the upper cervical nerve roots in monkeys (Magnus, 1918). In the midbrain or thalamic animal, to which attention will now be directed, similar reactions can also be demonstrated, but they are complicated by the presence of the righting reflexes.

MIDBRAIN AND THALAMIC ANIMAL

DECORTICATE RIGIDITY OF CAT AND DOG. In cat and dog distribution of tone is essentially normal *so long as the animal is on its feet*, but when suspended a strong hyperextended posture is assumed (Girndt, 1926). This has been recently studied in chronic decorticate cats by Bard and Rioch, who write (1937, pp. 109-110):

"All four cats exhibited a nearly normal distribution of muscular tone while standing, sitting or crouching. The legs of each, however, became rigidly extended and strongly resisted passive flexion when the animal was held suspended in any position. The intensity of this extensor hypertonia was comparable to that of the average decerebrate preparation. Unlike decerebrate rigidity, however, it was revealed in full strength only when the animal's feet were freed from the function of supporting the weight of the body. Thus it appeared in a hindleg that was held forward along the side of the body as the animal squatted on the other three legs; it was displayed in legs which were allowed to hang over the edge of a table upon which the animal rested; and it was invariably found in dependent forelegs which failed to place when the chin was put on some supporting surface. In the dorsal decubitus it was usually stronger in the hindlegs than in the forelegs. Characteristically the rigidity of any leg disappeared whenever that member engaged in any phasic activity and its distribution could be modified by the operation of the tonic neck and labyrinthine reactions. Following the first ablation it was found in the contralateral extremities only. This extensor rigidity was of the same intensity in the four cats and remained undiminished throughout their survival periods."

Liddell (1938a&b) emphasizes that the quality of the rigidity in the cat differs following a cortical extirpation from that encountered in the decerebrate state, the former being more plastic in character.

Decorticate primates, on the other hand, are unable to walk, and they assume a particular reflex attitude — a decorticate rigidity — which will

require separate description below. Attention will first be directed briefly to the effects on posture of labyrinthectomy in normal and in decerebrate animals.

GENERAL EFFECTS OF EXTIRPATION OF LABYRINTHS. The labyrinths are organs of special sense whose functions will be described in detail in another volume of this series. Excellent recent summaries are to be found in the monographs by Camis (1930) and by Dusser de Barenne (1934). It has long been known that unilateral ablation of the labyrinths causes an abnormal asymmetrical posture of the head and trunk, owing to unequal influence of the remaining labyrinths upon the neck muscles. A continuously acting stimulus to the righting reflexes develops in the remaining labyrinth causing body curvature, and under the continued stimulus animals at first tend to roll over and over. Dow's (1938) recent study of the effects of unilateral and bilateral labyrinthectomy in monkey and chimpanzee allows one to infer that the symptoms of labyrinthectomy become progressively less conspicuous as one ascends the evolutionary scale. Cold-blooded vertebrates are much disturbed by unilateral ablation of the labyrinths. Rabbits, cats and dogs are rather less disturbed. Monkeys and baboons have transient asymmetry of posture and the chimpanzee, like man, has slight asymmetry of posture, but none of the forced movements of the lower animals.

Removal of the labyrinths from a decerebrate or decorticate animal destroys both the labyrinthine acceleratory reflexes of eyes, neck and limbs (semicircular canals), and the labyrinthine positional reactions (static and righting arising in otolithic macula). Loss of these reflexes leads to three prominent symptoms: (i) absence of head righting reflexes, (ii) generalized diminution of resting postural contraction and (iii) absence of postrotatory nystagmus. These symptoms are easily recognizable after labyrinthectomy in monkeys which have previously been reduced to the thalamic reflex pattern. Particularly marked is the generalized diminution of resistance to passive manipulation of the entire musculature, especially that of the neck. The labyrinth thus appears to give greater intensity to all of the postural reflexes. It diminishes, but does not abolish, the intensity of the grasp reflex (Fulton and Dow, 1938).

RIGHTING REFLEXES. Righting reflexes of intact animals have attracted the attention of physiologists from the earliest times and various ingenious modes of analysis have been brought to bear upon the problem. Marey (1894) was probably the earliest to introduce motion picture photography for ascertaining the series of movements which a cat executes when righting itself in mid air, after being released upside down. By this method the actual muscular mechanics, the lateral curvature of the back and the inevitable turning which follow, were accurately described. But it remained for Magnus and his collaborators to analyze the individual reflexes which make these movements possible, and, with Rademaker, to determine the part of the brain stem in which they are integrated. There are five groups of reflexes arising as follows: (i) in the labyrinths, (ii) from body to the head, (iii) from the neck, (iv) from body

to the body and(v)from the eyes. In order to determine the contribution of each one, it is necessary to reduce an animal to the so-called "zero condition" for righting, *i.e.*, by destroying a sufficient number of sensory sources of righting so that the animal shows no tendency to right itself. The zero condition for a thalamic animal occurs if both labyrinths are destroyed and the body is held away from the ground with eyes blindfolded(cats, dogs and monkeys). This causes the animal to be completely disoriented and it thus makes no effort to bring its head or body into normal position.

Labyrinthine righting reflexes. If an animal is held blindfolded in the zero condition and its labyrinths are allowed to remain intact, the head tends to assume the horizontal position, irrespective of the position in which the body, or any part of the body, is placed. These reflexes of the head disappear entirely when both labyrinths are extirpated. They also disappear if the otoliths are detached by centrifuging. The asymmetrical righting reflexes are evoked from the *maculae sacculi*, for after unilateral labyrinth extirpation the resting position of the head is no longer the normal position, but rather the lateral. Magnus argued that the *utricle maculae*(fig. 47) can not be responsible for this reflex, since the maculae concerned could not lie in one plane. The saccular otolith pulls the maculae when one labyrinth is ablated, and the head comes to rest when the intact saccular macula is in the minimum position, *i.e.*, with the otolith pressing upon the saccular macula in the horizontal plane. The labyrinthine righting reflexes thus give the head orientation in space. Since the position of the head through operation of the tonic neck reflexes does much to determine the total posture of the body, the labyrinthine righting reflexes assume a position of primary importance.

Body righting reflexes acting upon head. Starting again from the zero condition, with a labyrinthectomized blindfolded animal held in the lateral position, the head will also be in the lateral position. If the animal is now placed on a table, the head becomes rotated immediately into the horizontal plane. The reaction has been traced to asymmetrical stimulation of the body surface which can be readily demonstrated by placing a weighted board upon the upper side of the animal so that pressure from each side is the same. In these circumstances, the head falls once more into the lateral position. Thus the head is normally oriented with regard to the ground by such stimulation, which no doubt plays an important role in the correction of abnormal postures of the head. The reflex is one acting synergically with those arising from the labyrinths.

Neck righting reflexes. The righting reflexes arising in the neck muscles tend to orient the body in relation to the head. Thus when, through action of the labyrinthine and body righting reflexes, the head is caused to assume a normal horizontal position, while the trunk is in the abnormal lateral position, the neck muscles are thereby twisted. This activates a chain of reflexes whereby the thorax is first rotated into the horizontal position, followed by the lumbar region and finally the hind quarters. All these reactions can, in point of fact, be seen in an intact animal if held in mid air and the pelvis caused to assume a different position. The head is first brought into the normal position and the forepart of the body quickly follows it. The action of other related tonic neck reflexes can generally also be demonstrated in this manner.

Body righting reflexes acting upon body. If an animal is held in the lateral position with force applied to the head and shoulders but not to the hind quarters, the body tends to right itself, the hind quarters first, in spite of the tendency of the neck muscles, in these circumstances, to keep the body on its side. The receptors for the reflex are again the sensory nerve endings of the body surface; they can be counteracted by a weighted board applied to the other side of the body, in which case the tendency of the hind quarters to assume a horizontal position promptly disappears.

Optical righting reflexes. The optical righting reflexes are absent in the thalamic or midbrain animal, since they depend upon the integrity of the occipital lobes. They are present, however, in the bilateral motor and premotor monkey (ch. XXI). During examination, the labyrinthectomized animal is held blindfolded in mid air. In these circumstances, its head is completely disoriented; but, if the eyes are allowed to see, the head is brought to a normal position as soon as the animal can focus upon some object in its environment. The centres essential for these reactions presumably lie in the calcarine cortex (ch. XVII). "The integrity of every single factor of this complicated function is doubly ensured. The head is righted by labyrinthine, tactile, and optical stimuli; the body by proprioceptive and tactile stimuli . . . The orientation of the head and body takes place in relation to gravity, sustaining surface, distant environment (optical), and in relation to parts of the body — a very complex combination of reflexes" (Magnus, 1926).

RIGHTING REFLEXES IN THALAMIC PRIMATE. Since thalamic monkeys are unable, like dogs and cats, to walk about (with normal tone) after their cerebral hemispheres are removed, their postural status must be separately considered. Karplus and Kreidl (1914) had described the posture of the rhesus macaque following removal of the cerebral hemispheres, but, since the work of Magnus had then only just commenced, they were not able to interpret their findings in the light of his disclosures. In 1922 Magnus described a characteristic postural pattern assumed by decorticate monkeys, which varied in predictable fashion with the animal's position in space. Thus, when lying in the lateral position, the monkey's undermost extremities are rigidly extended, while the uppermost extremities are strongly flexed. Turning the animal on its opposite side promptly reverses the pattern so that the extremities which were previously uppermost and flexed now become extended; the others become flexed (fig. 49). When lying on its side, the animal's posture of the extremities can be made symmetrical by placing a board against the lateral surface of the body so as to equalize cutaneous stimulation ("board test").

The same postural pattern appears in monkeys in which the motor and premotor areas have been ablated from both sides (Bieber and Fulton, 1938); furthermore, the uppermost flexed extremities exhibit the

grasp reflex, whereas the undermost extended extremities fail to do so (cf. ch. xxi). Fulton and Dow (1938) find the same thalamic pattern in somewhat less intense form after bilateral destruction of the labyrinth in these semidecorticated monkeys. In these circumstances tonic neck reflexes are readily demonstrated, *and the grasp reflex is invariably seen in those extremities which, through operation of the tonic neck and righting reflexes, assume a flexed posture.*

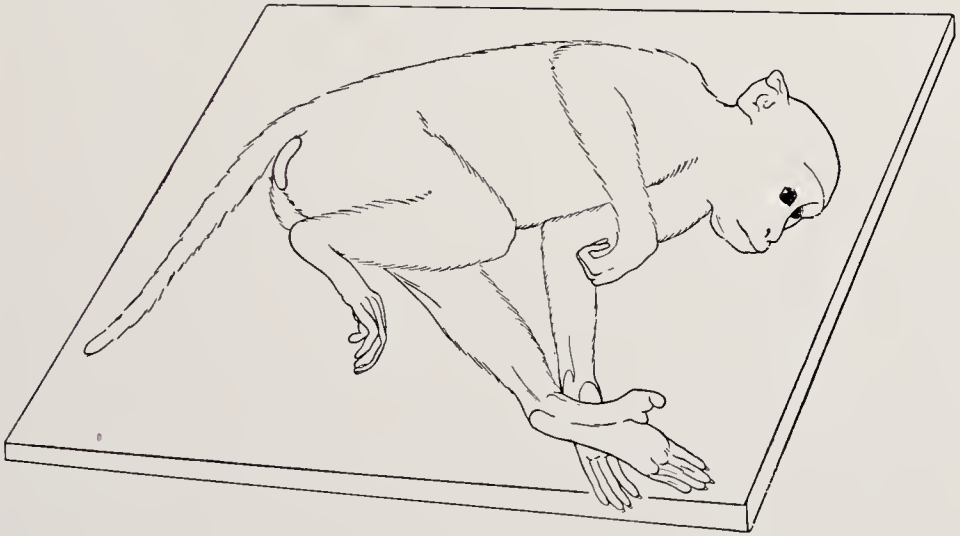


FIG. 49. Outline of a monkey in thalamic reflex status. Uppermost extremities are flexed and show grasp reflex, while undermost are extended and show no trace of grasping (Bieber and Fulton, *Arch. Neurol. Psychiat.*, 1938, 39, 435).

CENTRES FOR RIGHTING REFLEXES. The centres essential for the integrity of the four groups of righting reflexes present in the midbrain animal are still to some extent under discussion. The evidence of Rademaker (1931), however, points to the region of the brain stem, which contains the large-celled part of the red nucleus (chs. ix, xxv, fig. 41) as being essential. Thus section of the anterior half of the anterior colliculi just ahead of the point of emergence of the 111rd nerve does not interfere with righting reactions, whereas section of the brain stem a few mm. caudally *i.e.*, behind the origin of the 111rd nerve, destroys the labyrinthine and body righting reflexes. On the other hand, neither ablation of the dorsal half of the midbrain nor removal of the entire cerebellum has any influence on these reactions, all of which points to an active focus in the ventral part of the midbrain. If the brain stem is split in the midline, the righting reflexes still continue to be present until the decussation of the

rubrospinal tracts are severed. Rademaker(1926)stated that he was able to destroy the substantia nigra on both sides without interfering with the righting reactions. Magnus, at the time of his death, was firmly convinced, in view of Rademaker's evidence, that the red nuclei were in fact the centres for the labyrinthine righting reflexes and of the body righting reflexes which act upon the body, and that the efferent tract involved was the rubrospinal. He believed the body righting reflexes acting upon the head had their centres at the same level, but not in the red nuclei. The optical righting reflexes are clearly cortical and neck righting reflexes bulbar. More recent evidence has tended to place all righting reflexes outside the red nucleus in the reticular substance at the same level.

Some of the criticisms of Rademaker's conclusions offered by Ingram and Ranson(1932a&b)and Keller and Hare(1934)do not appear to be entirely relevant (see Rademaker, 1937), since these authors have not repeated the actual experiments of Rademaker and Magnus. They find in the otherwise intact animal that complete destruction of both red nuclei does not abolish the righting reflexes. This, together with other evidence presented in the paper of Ingram, Ranson and Barris (1934), demonstrates that the red nucleus itself cannot be responsible for the labyrinthine and body righting reflexes; their work, taken with that of Magnus and Rademaker, proves, however, that the righting reflexes must be integrated *at the level of the red nucleus*(fig. 50, ch. xi). Ranson and his collaborators suggest that they are mediated by the surrounding reticular substance of the tegmentum and that the red nuclei themselves are entirely taken up with cerebellar reactions. Ingram, Ranson and Barris point out that complete and isolated destruction of the red nucleus causes some increase in extensor tonus, ataxic disturbances of gait and augmentation of the positive supporting reaction. Postural reactions, such as the shifting reflex, are also impaired. Since all of these disturbances are seen following decerebellation, they conclude that they are essentially disturbances of cerebellar outflow.

POSTURAL REFLEXES DEPENDING UPON CEREBRAL CORTEX

The recent investigations of Philip Bard and his various collaborators (cf. Bard, 1933; Bard and Brooks, 1934; Woolsey, 1933 and Bard, 1936) have shown that the placing and hopping reactions depend upon the integrity of the motor areas of the frontal lobes, both in cats and monkeys. These reactions have been graphically termed "cortical reflexes." They are of great value in testing the integrity of the sensory and motor pathways after experimental lesions(cf. ch. xix and xx).

PLACING REACTIONS. These reactions which were first studied by Rademaker in 1931 consist of a postural adjustment of the limbs brought about in anticipation of contact with a solid object, *i.e.*, the foot is put

down in such a way that without further postural change it can support the weight of the body. With vision excluded, various exteroceptive and proprioceptive stimuli arising from contact, as well as from movements, serve to evoke the response. Bard (1941) describes five nonvisual placing reactions as follows (cf. also Barris, 1937a&b):

1. If a cat is held in the air with the legs free and dependent and with the head held up (so that it cannot see its forefeet or any object below and in front), the slightest contact of the back of either pair of feet with the edge of a table results in an immediate and accurate placing of the feet, soles down, on the table close to its edge. This is "contact placing."

2. If the forelegs of a cat suspended in the air are held down, and the chin is brought in contact with the edge of a table, both forefeet on being released are instantly raised and placed beside the jaws. Usually this is followed by extension, so that a standing position is quickly assumed. If a blinded animal is used, the forefeet, even though not held down, remain hanging until the chin touches the table. This is "chin placing."

3. If the forelegs or hindlegs of a cat that is standing, sitting, or crouching on a table, are thrust over the edge, they are immediately lifted so that the feet quickly regain their original positions on the table.

4. If any leg of a standing cat is passively abducted without being held, it is at once adducted and lowered so as to restore the foot to its normal standing position.

5. Although each of the foregoing reactions may be adequately studied in animals with vision intact, this final one can be evoked in pure form only after blindfolding, enucleation of the eyes, or removal of the visual cortex. The animal held in the air with the forelegs free is moved toward some solid object. As soon as the tips of the vibrissae of one or both sides touch the object, both forefeet are accurately placed on it. Unless the influence of the eyes is excluded, a visual placing reaction of the forelegs will be evoked under these circumstances.

6. A further reaction is useful in separating sensory and motor components. If the foot making contact with the table is restrained, the opposite limb places. This is the "crossed placing" reaction.

HOPPING REACTIONS. Hopping reactions are essentially corrective movements of the limb which strive to maintain a standing posture under conditions involving displacement of the body in the horizontal plane (Bard). To evoke the response the animal is made to stand on one leg and then the body is caused to move forward and backward, or from side to side. In these circumstances the animal executes a series of hops. Bard gives reason for regarding these reactions as myotatic in origin. Both groups of reactions are of considerable interest because of their dependence on the cerebral cortex.

SUMMARY

Two large groups of reactions affecting skeletal muscle are mediated in the brain stem: the postural reflexes and the righting reactions. Although all phases of the postural mechanism are influenced by the cerebral cortex — some reflexes such as the hopping and placing reactions actually depend upon its integrity — many basic reactions are integrated in the medulla oblongata (vestibular nuclei); the righting reactions, on the other hand, owe their integrity to the midbrain, but the nuclei, upon which they depend, have not been ascertained.

The postural reflexes are made up of: (i) local static, (ii) segmental static and (iii) general static reactions. The local static reactions are those which tend to affect single extremities, the positive and negative supporting reactions being generally grouped in this category. These become accentuated in an otherwise intact animal after removal of the cerebellum, and they can also be demonstrated in the midbrain and probably in the chronic oblongata preparation. The adequate stimulus has two components: contact with the skin of the foot plus (in the dog) separation of the toe pads. The reaction is one which fixes all joints in a rigidly extended posture adequate to support the animal's weight. The negative supporting reaction is evoked by flexing the distal points, and it consists of inhibition of the extensor posture just described.

The segmental static reactions are those in which a stimulus to one extremity affects the fellow extremity of the opposite side such as the crossed extensor reflex; also the shifting reactions, which consist of an extension reflex in one limb when the body, supported by the opposite limb, veers towards the side of the limb under observation.

General static reactions have to do with reflexes arising in one segment, affecting muscles innervated by other segments, and more particularly with the tonic neck and labyrinthine reflexes. After destruction of the labyrinth, tonic neck reflexes are brought out by rotation of the head which causes extension of the "jaw" limbs and flexion of the opposite; deviation of the head without rotation does the same, while dorsiflexion of the head evokes extension of the forelimbs, and relaxation of the hind (attitude of a cat looking upward); ventroflexion of the head elicits flexion of the forelimbs and extension of the hind. These reactions are found in oblongata dogs and cats, and in midbrain monkeys and human beings. In primates, including man, the grasp reflex

is a part of these postural reactions and it is always present in the flexed limb and absent from the extended.

Tonic labyrinthine reflexes can be observed in decerebrate animals when the neck reflexes are excluded by section of the upper three pairs of dorsal cervical nerve roots. Such preparations exhibit two groups of reactions: acceleratory and positional. The acceleratory reflexes arising in the semicircular canals give rise to a group of special reactions involving the eye (vestibular nystagmus) and the skeletal muscles; the reactions may be responsible in the intact individual for subjective symptoms of dizziness, etc. The positional reflexes arise from the otolithic maculae of the labyrinth, and have to do principally with the righting reflexes, the majority of which are integrated in the midbrain.

Righting reactions have to do with a chain of reflexes which operate to bring, or to maintain, an animal right side up with the universe. In the case of the three-toed sloth, the right-side-upness happens to be belly to the heavens; in man, vertex to the stars, etc. Right-side-upness is made possible by five groups of reactions. Since they are but briefly summarized in the text, only the names need be given here: (i) labyrinthine righting reflexes, (ii) body righting reflexes acting upon the head, (iii) body righting reflexes acting upon the body, (iv) neck righting reflexes and (v) optical righting reflexes. The first three depend upon the integrity of the midbrain at the red nucleus level, but not upon the red nucleus itself. The neck righting reflexes are integrated in the medulla and the optical in the cortex.

The hopping and placing reactions, also important in the postural group, depend upon the integrity of the motor areas of the frontal lobes (ch. xx).

XI

THE PONS AND MIDBRAIN: OPTIC REFLEXES

HISTORICAL NOTE

The response of the pupils to the action of light is mentioned by many early writers, but Robert Whytt, the neurophysiologist of Edinburgh, in a remarkable book entitled *Essay on the vital and other involuntary motions of animals* published in 1751, was the first to prove that it was a reflex ("Whytt's reflex"). He described the pupillary response at length, mentioning that its afferent pathways lie in the optic nerve and its efferent pathways in the third pair and finally that the integrity of the thalamic region is essential to the reaction. He based this important conclusion upon the case of a child who, prior to death, had a fixed pupil. At autopsy a cyst was disclosed which had compressed the thalamus. Thus, Whytt (1751, p. 131) says: "From this remarkable history, it seems manifest, that the dilatation of the pupil soon after the coming on of the *coma*, was owing to the compression of the *thalami nervorum optitorum*, by the water collected in the brain, which rendered the *retina* insensible to the *stimulus* of light." Although the physiology of pupillary dilatation and constriction had been studied by Magendie and Claude Bernard, the next discovery of importance was made in 1869 by Douglas Argyll Robertson. Independently of Horner whose description of cervical sympathetic ptosis was published in the same year, Argyll Robertson revealed the effect of spinal injuries on the pupil. Robertson's second paper (1869b) entitled "Four cases of spinal myosis; with remarks on the action of light on the pupil," describes four patients who evidently had locomotor ataxia. "In all," he says, "there was marked contraction of the pupil which differed from myosis due to other causes (*e.g.*, Horner syndrome) in that the pupil was insensible to light, but contracted still further during the act of accommodation for near objects." This paper was published before syphilis of the nervous system had been described. Since 1869 the pupil which reacts to accommodation and not to light — the "Argyll Robertson pupil" — has been a subject of perennial discussion, particularly from the point of view of localization of the lesion responsible for the symptom complex. A summary of the pathological literature was given by Sven Ingvar in his Herter Lecture (1928). More recent physiological evidence will constitute part of the ensuing chapter (see Langworthy and Tauber, 1937).

IN a systematic presentation of functions of the brain stem, one should proceed logically from the medulla oblongata (myelencephalon) to the pons and cerebellum (metencephalon). Since, however, the functions of the cerebellum are best understood after discussion of the cerebral cortex, and since the pons itself has few nuclear masses, except for the pontine nuclei which connect the cerebellum with the cerebrum (and the nuclei of cranial nerves v[in part] and vi), consideration of the met-

encephalon will be deferred to chapter xxv. In the present chapter certain phases of function of the midbrain, or mesencephalon, will be described, particularly reflexes involving the eye. The mesencephalon includes the following nuclear masses: the nuclei of 11rd, 14th and part of 5th cranial nerves, the superior and inferior colliculi, red nucleus, substantia nigra, and the nuclei of the posterior commissure and medial longitudinal bundle. In addition the reticular substance surrounding these nuclear masses contains motor cells and neurons which have motor functions.

EFFECTS OF STIMULATION

The functions of the quadrigeminal region (dorsal mesencephalon) were first studied by electrical stimulation. There is a full account of early disclosures in Sherrington (1900c, pp. 911-916). In cold blooded animals the mesencephalic roof is an active motor centre, which, on stimulation, yields movements of the tail and fins in fish, movements of the head and vocalization in the frog, and in birds and rabbits, movements of the eyes and dilatation of the pupil. In the dog, conjugate lateral deviation of the eye follows stimulation of the anterior corpora, and from the posterior part elevation of the eyes and dilatation of both pupils. (The latter disclosure is important, since in pineal tumours which directly compress this area paralysis of upward deviation is an early symptom). In the monkey Ferrier (1876) found that excitation of the anterior corpora moved the eyes, as in the dog, towards the opposite side; it also caused opening of the palpebral fissures, elevation of the eyebrows, and head turning. From the posterior corpora Ferrier obtained vocalization.

Stimulation of the ventral mesencephalon causes alteration of posture of the extremities. Thus Graham Brown (1913) elicited movements similar to those following stimulation of the anterior lobe of the cerebellum, *i.e.*, he evoked inhibition of decerebrate rigidity on the side opposite and flexion responses on the same side. In 1915 Graham Brown stimulated the red nucleus of a chimpanzee; the decerebration had been carried out at the anterior level of the red nucleus and in these circumstances the upper extremities exhibited fairly strong flexor contraction (as in monkeys decerebrated above the red nucleus, Brown, 1915b; and also man, ch. ix). When the red nucleus was stimulated, the contralateral upper extremity became extended and the ipsilateral flexed. There was a good deal of variation, however, depending upon the intensity

and the exact point of application of the electrode. In a third paper of this series Graham Brown(1915c) reported his belief that he was able to evoke *reflex laughter* from the posterior part of the thalamus of a chimpanzee at a point lying just above and lateral to the red nucleus area. Disturbance of respiratory movements also emanated from the same region.

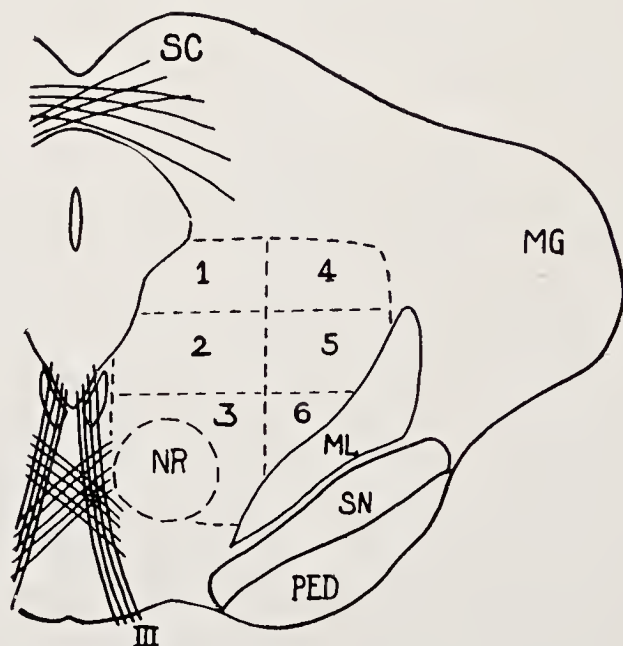


FIG. 50. Diagram showing the various reticular areas: 1, the dorsal medial reticular area, including the central tegmental fasciculus; 2, the middle medial reticular area; 3, the ventral medial reticular area; 4, the dorsal lateral reticular area; 5, the middle lateral reticular area; 6, the ventral lateral reticular area; SC, the superior colliculus; MG, the medial geniculate body; NR, the red nucleus; ML, the medial lemniscus; SN, the substantia nigra, and PED, the peduncle(Ingram, Ranson, *et al.*, *Arch. Neurol. Psychiat.*, 1932, 28, p. 524).

Direct stimulation of the red nucleus and the tegmental region(fig. 50)in a lightly anesthetized, but otherwise intact *cat* induces curving of the back towards the stimulated side associated with flexion of the ipsilateral forelimb; these responses have been attributed to cells in the reticular formation rather than to the red nucleus itself(Ingram, Ranson and Hannett, 1932).

In their next paper, Ingram, *et al.*(1932), state that manipulation of the tegmentum also causes "flexion of the ipsilateral forelimb and extension of the contralateral forelimb with varying movements of the hindlimb. In certain cases, parts of this response may be elicited; in others a variety of divergent reactions may

be added to it." The response pattern may be obtained from the caudal part of the subthalamus, from the reticular formation of the entire tegmentum (fig. 50); it could be followed from the reticular formation back to the caudal part of the pons where its foci then shift laterally towards the level of the trapezoid body. Ingram, Ranson and Barris (1934) insist that the response does not arise in the red nucleus, and they imply that it is probably mediated in part via the reticulospinal pathways. The red nucleus itself is primarily concerned with the cerebellar outflow (see ch. xxv).

LESIONS OF MIDBRAIN

Destruction of the colliculi in lower forms disturbs visual reflexes and in the bird may produce virtual blindness (Marquis, 1935). In the monkey, section of the brain stem at the anterior corpora, or between the two corpora, leaves intact reflex vocalization; transection behind the corpora quadrigemina abolishes it. Vocalization integrated at this level has a peculiar long-drawn-out quality and is often accompanied by slowly executed reflex movements (Sherrington, 1900b). Lesions of the superior colliculus of monkeys and baboons (Walker, 1940) cause conspicuous paralysis of the *pilomotor* reflexes on the side of the lesion. It has not yet been ascertained whether this is due to interruption of the tracts which pass superficially in the colliculi or to actual destruction of grey matter at that level. Quite superficial lesions suffice to provoke the symptom. After complete destruction of the superior colliculi in cats pupillary reactions to light remain normal in every respect (Keller and Stewart, 1932). When, however, there is coincident destruction of the pretectal region, the pupillary light reactions were completely abolished (Magoun, 1935, see below). These studies indicate that no part of the superior colliculus is concerned in the light reflex. The effects of isolated destruction of other parts of the mesencephalon, except for the red nucleus, have not yet been adequately studied.

PUPILLARY REFLEXES AND MIDBRAIN. Information concerning the central path of the pupilloconstrictor reflex is of particular clinical interest, since it should provide an anatomical basis for understanding the Argyll Robertson pupil and other disturbances of the pupillary innervation. For many years it was believed that the constrictor pathways passed centrally from the optic tract in the brachium of the superior colliculus and thence to the superior colliculus itself (Harris, 1935). The motor outflow was believed to go directly from there to the nucleus of the third nerve, but we have already seen that pupillary fibres do not reach the colliculus. In a series of papers from Ranson's Laboratory (1933-1937),

the actual course of the fibres involved in the light reflex was for the first time clearly established and the anatomical basis of the Argyll Robertson phenomenon further elucidated (cf. Barris, *et al.*; Magoun, *et al.*; Hare, *et al.*, and Atlas and Ingram). Their experiments may be summarized as follows:

The fibres mediating the light reflex of cats and monkeys have been followed by the Horsley-Clarke stimulator from the optic nerves *through* the medial border of the geniculates (fig. 51) and then, via the brachium of the superior colliculus, medially into the pretectal region *where they have their first synapse* (Hare, Magoun and Ranson, 1935). Lesions in the pretectal region of the cat's brain impair the pupillary reflex. In the case of bilateral lesions, the extent of the reduction appears to be proportional to the amount of pretectal area destroyed. With unilateral destruction, the contralateral eye is primarily affected. If, in addition to destroying the pretectal region on both sides, the anteromedial part of the superior colliculus is damaged, the light reflex is completely and permanently abolished. These lesions, however, do not actually produce an Argyll Robertson pupil, since reaction to convergence or accommodation could not be established in any of their experiments. Myosis from acute lesions lasts only a few days. In the chronic stage the pupils become widely dilated, owing to obliteration of the light reflex. In discussing the Argyll Robertson phenomenon, Magoun and Ranson were unable to decide whether it is due to chronic irritation of some part of the pupilloconstrictor path, or to an associated lesion in the pupillodilator pathway. They pointed out that it would be difficult for both mechanisms to be interrupted by a lesion of moderate size. After destruction of the posterior commissure of the midline, consensual light reactions of the cat are reduced, but not abolished. This indicates a partial decussation of the light reflex pathway in the commissure (fig. 51).

Path of light reflex. The course taken by afferent impulses involved in the light reflex is therefore as follows: Passing from the retina by the optic nerve to the optic tract, the fibres traverse the medial border of both geniculates into the brachium of the superior colliculus and thence into the pretectal region (transitional area between thalamus and midbrain) where they have their *first synapse*; a few fibres may terminate in the medial part of the anterior corpora. The cells on which the primary neurons terminate are not yet established (Atlas and Ingram, 1937b). In cats the majority of fibres (second order neurons) cross in the posterior commissure and then curve ventrally close to, or through, the central grey of the aqueduct to reach the Edinger-Westphal division of the 111rd nerve nucleus. In the cat some fibres do not cross in the commissure, but go directly to the 111rd nerve nucleus on the same side. In primates there is probably less crossing than with cats. From the Edinger-Westphal nucleus the efferent neurons take origin and pass by the 111rd nerve to reach the pupil.

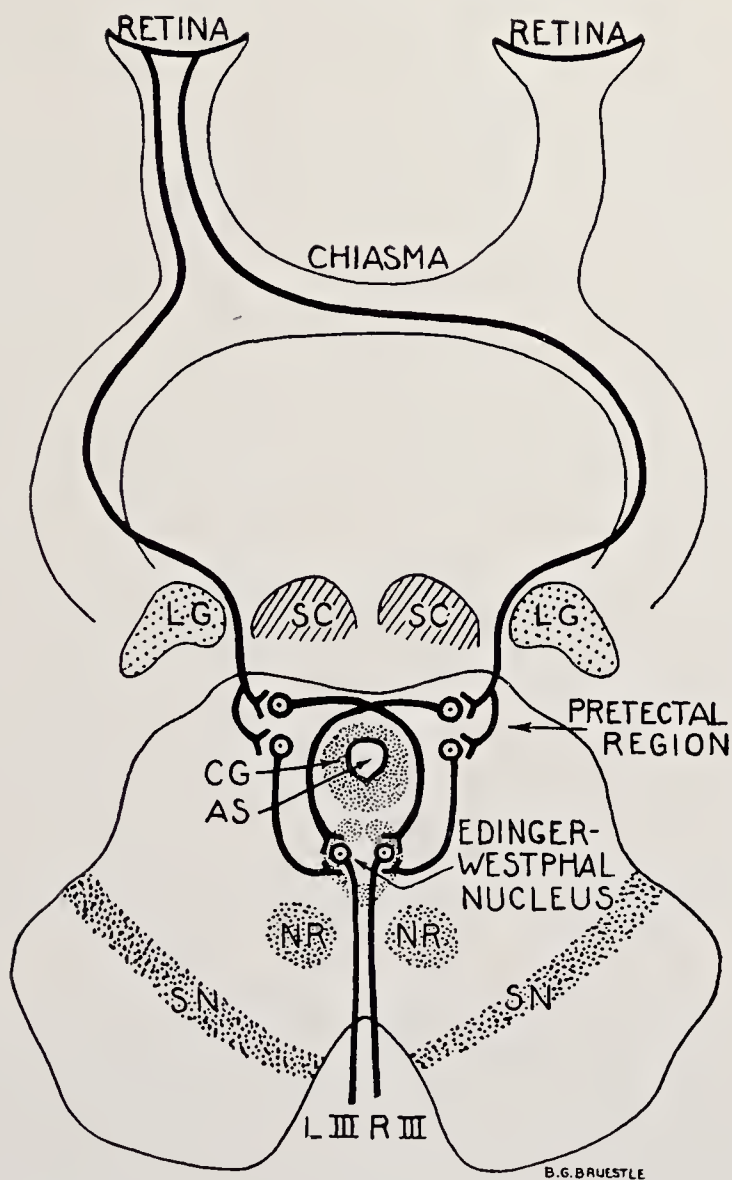


FIG. 51. Pathways involved in reflex response of pupils to light. Two neurons are shown arising in left retina which pass medial to both lateral geniculate bodies (LG) and brachia of superior colliculi (SC) to pretectal region whence neurons of the second order arise and pass close to the central grey, terminating in the Edinger-Westphal nucleus (see text); NR, red nucleus; SN, substantia nigra.

Area 19 of the cortex sends pupilloconstrictor fibres directly to the pretectal region to form synaptic connections with the second order neurons of the light reflex (Barris, 1936; ch. xvii). It is not yet known whether the corticotectal fibres terminate upon the same neurons as those from the retina. The Argyll Robertson phenomenon is due to involvement of fibres "upstream" from the Edinger-Westphal nucleus, since this is the sole origin of fibres giving active pupillary constriction. Some investigators have believed that the second order neurons are caught as they pass along the wall of the aqueduct; others have suggested (Sven Ingvar, 1928) that afferents of the light reflex pass superficially on the medial side of the optic tract and are affected by the basal meningitis of syphilis. This would account for the absence of the light reflex with integrity of the cortical convergence reaction.*

Oculomotor nerve. Section of the oculomotor nerve produces the familiar syndrome of ophthalmoplegia, consisting of complete closure of the eyelid on the same side, dilatation of the pupil (paralysis both of the light reflex and of convergence) and paralysis of internal, inferior and superior recti and the inferior oblique muscles. If the third nerve is sectioned as it passes along the sella turcica, in chimpanzees or monkeys, the nerve may regenerate in about three months with recovery of motor power of the lids and some recovery of extraocular movements. The pupil remains completely unresponsive to light even after four months, suggesting that the pupillary fibres do not readily regenerate (Bender, 1938).

Pseudo-Graefe phenomenon. During regeneration of the third nerve a stage is reached in which the formerly ophthalmoplegic eyelid fails to droop when the gaze is directed downward. In the mistaken belief that the mechanism was similar to that of the lid lag of exophthalmos, it has been referred to as the pseudo-Graefe phenomenon (Bender, 1936). Accompanying this eyelid symptom there is generally inward rotation of the globe and sometimes constriction of the pupil. The lid may not only fail to droop when the gaze is directed downward, but it may actually retract. This group of symptoms is due to indiscriminate regeneration of the oculomotor fibres into other muscles than those which they originally supplied. Except for the pupillary response, all of the manifestations of aberrant regeneration have been seen in experimental animals including the chimpanzee (Bender and Fulton, 1938).

* Foerster, Gagel and Mahoney (1936) find that ablation of the ciliary ganglion abolishes the light reflex, but not the pupillary constriction of convergence; since section of the third nerve destroys both, they conclude that the pupillary constrictors underlying convergence have a separate peripheral pathway, and therefore, presumably, a discrete origin in the third nerve nucleus (see also Levinsohn, 1909).

OTHER OCULAR REACTIONS

For an enumeration of the numerous ocular reflexes known in man the student must turn to current texts of clinical Neurology; one need only mention the corneal reflex, the blink reflex, the pain reflex of the pupil(dilatation), all of which repay careful study. The central pathways of such clinical reflexes affecting the eye have not been carefully worked out as have those of the light reflex, but it is believed that they all involve either the midbrain or hypothalamus and sometimes both. Thus the corneal reflex is mediated by the vth nerve on the afferent side, while its motor pathway emerges through the viith. The corneal reflex is widely used as an index of the depth of anesthesia; it should be realized, however, that it is applicable only to the depth of anesthesia induced by the volatile anesthetics such as ether and chloroform. The barbituric acid anesthetics such as dial and amytal, which act specifically upon the midbrain and hypothalamus, abolish the corneal reflex often before consciousness is suppressed. Hence the corneal reflex is not a reliable index of the depth of surgical anesthesia when a barbiturate is used as the anesthetic agent.

The coördination of ocular movements and the central pathways involved also belongs to a special field of Neurology which can not be treated in a general text. For an excellent account of the neurology and neurophysiology of the extraocular movements the study of Riley (1930) should be consulted.

SUMMARY

The mesencephalon, or midbrain, includes the region of the brain stem lying between the diencephalon(thalamus and hypothalamus)rostrally and the pons caudally. It includes the iird, ivth and vth cranial nerve nuclei, the colliculi, red nucleus, reticular substance, substantia nigra and many ascending and descending fibre tracts.

Faradic stimulation of the quadrigeminal region evokes motor movements in the lower animals, but in mammals responses are largely limited to the eye and head(head turning), and include, from the anterior corpora, dilatation of pupil and conjugate movement of the eyes to the opposite side. Pupillary constriction is obtained only from the pretectal region. Destruction of the corpora quadrigemina causes pilomotor paralysis and paralysis of upward movement of the eyes and other ocular

disturbances, but *it does not abolish the reflex response of pupil to light.*

From stimulation of the ventral mesencephalon one obtains slow tonic movements of the extremities, inhibition of decerebrate rigidity homolaterally (flexion of the limbs), and increased extension of the contralateral extremities. When the red nucleus itself is stimulated in primates, the upper extremities, which are flexed in the decorticate posture, become extended contralaterally and flexed ipsilaterally.

Isolated stimulation of red nucleus and of surrounding reticular substance in the lightly anaesthetized intact animal causes curving of the trunk and a variety of other tonic movements. Isolated destruction of the red nucleus does not abolish these reactions to stimulation.

The pathways involved in the light reflex of the pupil have been traced by focal stimulation of the brain stem and by focal destruction, both executed with the Horsley-Clarke stereotaxic instrument. The fibres involved arise in the retina and pass in the optic tract along the medial wall of the lateral geniculate body through the brachium of the superior colliculus and establish their first synapse in the pretectal region. The second order neurons then pass close to the central grey of the aqueduct to the Edinger-Westphal division of the third nerve nucleus where the third nerve pupillary constrictor fibres arise.

The clinical syndrome of the Argyll Robertson pupil in which the light reflex is abolished and pupillary contraction on convergence remains has not yet been reproduced experimentally.

XII

AUTONOMIC NERVOUS SYSTEM *

- HISTORICAL NOTE

From almost the dawn of medicine, medical thought has dwelt on the possible implication of the visceral nerves in disease. Galen's hypothesis of the generation of animal spirits by the brain offered the first widely accepted interpretation of the phenomenon of "sympathy" or "consent." Wherever peripheral nerves joined, communications were thought to exist, thus allowing the animal spirits to flow with ease from one part of the body to another, and thereby accounting for the appearance of symptoms in one organ consequent upon disease in another. The description of the "sixth pair" of cranial nerves, given by Galen, and followed by all physicians up to and including Vesalius, grouped the vagus nerve and the ganglionated trunk of the sympathetic system as one, both anatomically and physiologically. Estienne(1545) and later Eustachio(1552, published 1714) were the first to distinguish the two nerves anatomically, but Eustachio ascribed to the sympathetic component an intracranial origin. This unfortunate error was perpetuated by Willis(1664), who, however, recognized the connections with the spinal cord, for he gave to the ganglionated chain the name "intercostal" nerve, "because passing near the roots of the ribs it receives in every interspace a branch from the spinal marrow."

Willis was one of the first to introduce into scientific thought the concept of "involuntary" as distinct from "volitional" movement, and in 1751 the brilliant Edinburgh physician, Robert Whytt, developed this idea into our earliest concept of reflex action, clearly recognizing the importance of the appropriate "adequate" stimulus for each organ. Whytt drew attention to the existence of nerve fibres as single units, in contradistinction to the older view of anastomosing channels, and argued that all sympathy therefore "must be referred to the brain itself and spinal marrow." In 1727 the French surgeon, Pourfour du Petit, cut the "intercostal" nerve in the neck and found that the disturbances occurred in the face and eye on the same side. He thus put to an end the view that the "intercostal" nerve was of cerebral origin. Du Petit's conclusions were accepted and supported with anatomical evidence by Winslow(1732), the Danish anatomist, who gave to the ganglionic chain its present name "grand sympathique," stressing thereby the belief that various remote parts of the body, were brought by it into "sympathy" with one another. Winslow's proposal to call the vagus the "moyen sympathique" and the facial nerve the "petit sympathique" has not been accepted. Since the supposed cerebral origin of the sympathetic chain had been disproved, and the significance of the rami communicantes not yet established, it was a logical deduction for Bichat(1800) to make that the sympathetic ganglia were nerve centres entirely independent of the central nervous system. Bichat divided physiological

* Revised for 2nd edition by Prof. Donal Sheehan of New York University College of Medicine, to whom I am greatly indebted. — J. F. F.

processes into "la vie organique" and "la vie animale," a distinction which exists today in the current ideas of "visceral" and "somatic" functions. He was the first to correlate the sympathetic nerves with the metabolic functions of the body, and the term "vegetative nervous system" was therefore used by his follower, Reil(1807).

Modern concepts of the autonomic nervous system begin with Remak, who in 1838 gave the first adequate account of the unmyelinated fibres, which he postulated arose from the cells in the sympathetic ganglia. In 1846 Beck differentiated clearly between the white and grey rami, on the grounds of their appearance and of the direction of their constituent fibres. The histological demonstration that the walls of blood vessels contain muscle, and were surrounded by a fine plexus of non-medullated fibres, laid the groundwork for the discovery of vasomotor nerves by Claude Bernard(1851)and Brown-Séquard(1852). Bernard went so far as to predict from his experimental evidence that the outflow of the vasomotor fibres would be found in the region of the spinal cord between the cervical and lumbar enlargements. Thus the physiologists began placing first the vasomotor, then the sudomotor and ultimately the pilomotor fibres within the thoracolumbar outflow as we know it today. Meanwhile the Webers(1845)had shown the inhibitory action of the vagus on the heart, Ludwig's classical paper(1851)on salivary secretion from stimulation of the chorda tymani had appeared, and Eckhard in 1863 had demonstrated a sacral outflow of vasodilators in the nervi erigentes. The ground was well prepared for the brilliant studies of Gaskell and Langley, upon which our present concepts of the autonomic nervous system rest.

Tracing the course of the fibres in ventral and dorsal spinal roots with the aid of the osmic acid technique, Gaskell(1885)at once appreciated the significance of the fine medullated fibres(under $3\ \mu$ in diameter)in the thoracolumbar ventral roots, following them through the white rami into the sympathetic chain. A similar outflow of fine myelinated fibres was observed in the vagus, glossopharyngeal and tympani nerves, and in the sacral spinal ventral roots. There appeared therefore to be three separate outflows, "bulbar," "thoracolumbar" and "sacral," which Gaskell later(1916)grouped together under the term "involuntary nervous system." Gaskell was probably the first to postulate the existence of two antagonistic systems of nerves for the control of involuntary muscular activity and glandular secretion, one excitatory and the other inhibitory. In Gaskell's concluding remarks(1885) one finds the link between Bichat's "organic" nervous system and Langley's subsequent classification into "sympathetic" and "parasympathetic" divisions. "The evidence is becoming daily stronger that every tissue is innervated by two sets of nerve fibres of opposite characters, so that I look forward hopefully to the time when the whole nervous system shall be mapped out into two great districts of which the function of the one is katabolic, of the other anabolic, to the peripheral tissues."

In 1889 Langley(1893)began his work on the effect of nicotine on synaptic transmissions in autonomic ganglia. When nicotine is painted on a ganglion, or injected intravenously, synaptic transmission is temporarily facilitated and then completely blocked. By stimulation of fibres entering the ganglion it is possible thereby to determine whether they pass through it with or without synaptic interruption. By applying this discovery, Langley mapped out the exact distribution of most of the "preganglionic" and "postganglionic" nerves, which he thus named in 1893. In 1898 he introduced the term "autonomic nervous system" to include the cranial, thoracolumbar and sacral outflows, qualifying his suggestion by stating that 'the word 'autonomic' does suggest a much greater degree of independence of

the central nervous system than in fact exists." The discovery that epinephrine resembled closely in its effects those of the thoracolumbar outflow, and that other drugs, such as pilocarpine, cause effects similar to those produced by stimulation of fibres in the cranial and sacral outflows, led Langley in 1905 to group the latter fibres under the name "parasympathetic" nervous system, reserving the term "sympathetic" for the thoracolumbar outflow. For an adequate background of the subject the student is advised to consult the chapter on the autonomic nervous system by Langley in Schäfer's *Text-book of Physiology* (1900) and his incompleting monograph (1921) published shortly before his death. Historical surveys of the autonomic nervous system have been published by Langley (1916) and Sheehan (1936).

HOMEOSTASIS

SOMATIC nerves, which have thus far been considered, are concerned in the rapid responses of the organism to changes in its external environment. These repeated demands on the body musculature necessitate continual adjustments in the dynamics of the circulatory system, in respiratory and metabolic processes and in the activity of visceral organs. During muscular exercise, for example, there is an augmented blood supply and increased metabolism in skeletal muscle which require a shift in blood volume from one part of the body to another, and a consequent diminution in activity of organs which are temporarily less important in the immediate response. These rapid adjustments in visceral and vascular structures are brought about by means of autonomic nerves. There is no real separation, however, between somatic and visceral spheres. Visceral reactions are part of the organism's total adjustment to its environment, and probably every activity of skeletal muscle, even a slight shift in tonus, is accompanied by changes in the visceral field. The reverse is equally true. Increased visceral activity, which occurs during digestion, is accompanied by diminished circulation through the skin and voluntary muscles, and disorders in visceral activity may lead directly to somatic reactions, such as skeletal muscle spasm. Autonomic nerves therefore are in no way independent of somatic. The two are interdependent. This concept, the antithesis of that expounded by Bichat at the beginning of the last century, is made apparent by a consideration of the central nervous system, for here we find somatic and autonomic functions regulated from common levels, in the cord, brain stem, hypothalamus and cortex.

Autonomic adjustments, while allowing for necessary responses of the organism, must maintain a physiological state adequate for the needs of the tissues. Vascular changes accompanying muscular exercise must

take place without appreciably affecting the general blood pressure or body temperature. Otherwise the disturbances would offset any benefit from the particular response. The physiological requirements of any tissue must be balanced against those of all others, and with minor fluctuations, a steady "internal constitution" maintained. The constancy of the "milieu interieur," as Claude Bernard termed it, is a condition, not of static, but of dynamic balance: it is maintained at a price. Forces pulling in opposite directions are equilibrated so as to give an appearance of rest. The condition has been called *homeostasis* by Cannon, to whose extensive studies we owe our present understanding of its delicate balancing mechanisms. Innumerable examples of homeostatic balance can be recalled. The increased venous return to the heart caused by muscular exercise is accommodated by reflex acceleration of the heart and peripheral vasoconstriction, but a consequent rise in general blood pressure is immediately counteracted by increased activity of the aortic and carotid sinus reflexes. A warm external environment initiates reflex sweating and peripheral vasodilatation, with consequent increase in heat loss, but any tendency of the body temperature to fall will bring about shivering(heat production)and peripheral vasoconstriction(reduction in heat loss). *Rapid* adjustments of this kind are the functions of the autonomic nerves. Slower adaptations are, however, possible through chemical and hormonal influences, so that the autonomic system can not be considered as indispensable. For details of autonomic regulatory mechanisms, the student is referred to the recent monograph by Gellhorn (1943).

If the environmental situation is such that the life of the animal is threatened, as in meeting an enemy, exposure to severe cold, in anoxia or severe haemorrhage, all the resources of the body may be called upon, and a massive response may be required. In mobilizing the body for combat, the sympathetic component of the autonomic nervous system is thrown into full activity. Large quantities of adrenalin are thereby liberated into the blood stream. The sympathico-adrenal system is said to prepare the animal for "fight" or "flight." Thus it constricts the vessels of the skin and viscera, causing a shift of circulating blood to organs essential for struggle, such as skeletal muscle and heart, the blood vessels of which are dilated during full activity of the sympathetic system. Cardiac rate is accelerated, respiration deepened, gastrointestinal motility inhibited, the pupil dilated, the hair raised and the skin moistened

with sweat. The changes are the typical manifestations of a frightened animal. Sympathetic activity has therefore been regarded as an emergency mechanism. To restrict its function to such a narrow concept would be misleading. Autonomic adjustments are called into play at all times; even the simple act of standing upright is a mild emergency. Certain tissues, however, are under greater sympathetic control than others and the immediate results of removal of sympathetic innervation differ widely in various parts of the body.

The *parasympathetic* component of the autonomic system has been aptly characterized by Cannon as that concerned with the protection, conservation and restoration of the bodily resources. Thus the retina is protected from the effects of bright light by constriction of the pupil, and the heart from over exertion by inhibitory action of the vagus. All processes essential for digestion and absorption of foodstuffs, including salivation, secretion of gastric and pancreatic juices, peristalsis, and the liberation of insulin into the blood stream, are promoted by the parasympathetic. There is an obvious basic antagonism in the effects of sympathetic and parasympathetic activity. The subdivision of Gaskell into "catabolic" and "anabolic" systems has much to recommend it, but the total massive response, observed in the sympathetic system, is not found in the parasympathetic. The reactions are more restricted in localization. Furthermore, not all organs supplied by sympathetic fibres receive parasympathetic innervation. This will be evident from a brief summary of the structural features of the autonomic system.

GENERAL ANATOMY

The autonomic system can be defined as *that part of the nervous system innervating smooth muscle, and cardiac muscle and glands, e.g., the pituitary*. Unlike skeletal muscle which degenerates when its somatic nerve has been interrupted, smooth and cardiac muscles possess rhythmic contractility, which persists after all extrinsic autonomic nerves have been divided. They have therefore been called "involuntary" muscle, though the term is perhaps unfortunate, because skeletal muscle is under the control of the will in but a restricted sense, and involuntary muscle can be influenced directly from the cerebral cortex. Autonomic pathways exist in both the central and peripheral divisions of the nervous system. The central connections are so closely integrated with the somatic activities of the central nervous system that anatomical definition

and segregation is difficult. They will be discussed in greater detail in the following chapters.

Here we are concerned principally with the peripheral distribution of autonomic fibres, and more particularly with the efferent outflow. The sympathetic chain and vagus nerve obviously carry many *afferent* fibres, some sensory in nature, giving rise to visceral pain, and others involved

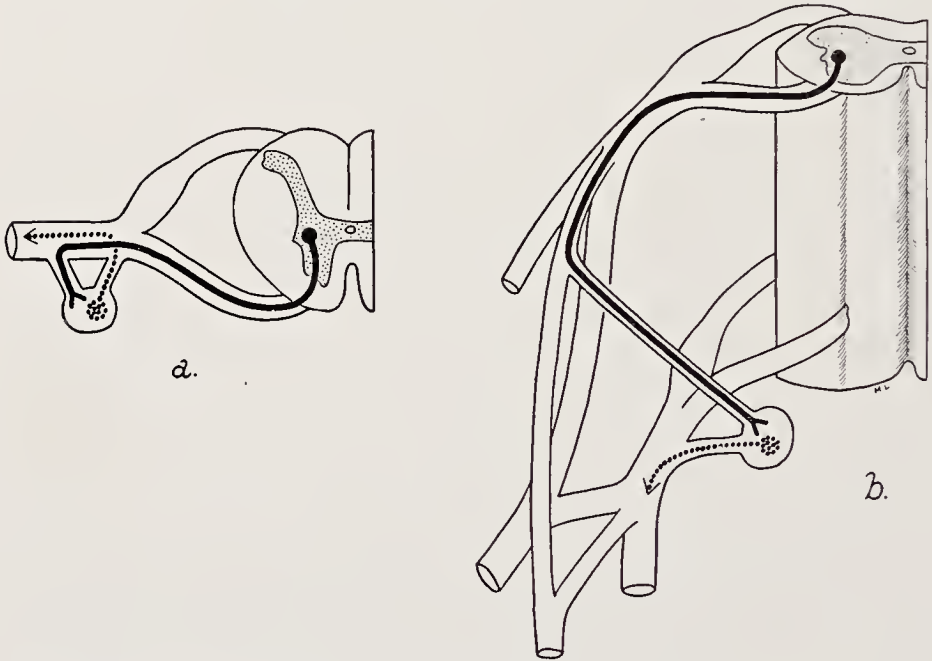


FIG. 52. Diagram showing arrangement of white grey rami(a)upper thoracic region, (b)upper lumbar region(Sheehan and Pick, *J. Anat.*, 1943, 77, 136).

in viscerovisceral and viscerosomatic reflexes that never reach consciousness. There is some question, however, whether such fibres should be classified as “autonomic,” the term adopted by Langley for a purely efferent outflow, and it is perhaps better to use the standard morphological term “visceral afferent.” Such fibres will be discussed later under a separate heading(see above, ch. 11).

Following Langley, the efferent peripheral pathways of the autonomic nervous system are generally classified in two divisions(i)the *thoracolumbar*(*sympathetic*)outflow, and(ii)the *craniosacral*(*parasympathetic*)outflow. In both subdivisions the pathway is characterized by and differs from the somatic in *having synaptic junctions which lie outside the central nervous system in peripherally located ganglia*. There is one synapse

along every path, involving *preganglionic* and *postganglionic* fibres. Along the sympathetic pathways the synaptic junctions usually lie in ganglia of the vertebral chain, or in ganglia embedded in the prevertebral plexuses (coeliac, superior and inferior mesenteric, etc.). Each preganglionic fibre, by its bifurcation, comes into synaptic relationship with many postganglionic neurons, an anatomical basis for *diffuse* responses throughout the body. The ratio of preganglionic to postganglionic neurons in the superior cervical ganglion in the cat was determined by Ranson and Billingsley (1918) as 1:32. Wolf (1941) found it lower, about 1:15. On the parasympathetic side the preganglionic fibres are relatively longer and do not synapse until they reach cells lying in ganglia close to or within the organ of supply. The ratio of pre- to postganglionic neurons in the ciliary ganglion in the cat is about 1:2 (Wolf, 1941). The arrangement is one more applicable to discrete responses in single organs.

SYMPATHETIC (THORACOLUMBAR) OUTFLOW: Preganglionic fibres arise from cells in the lateral horn of grey matter of the spinal cord. The fibres leave the cord with the ventral roots of the thoracolumbar region, from T₁ to L₂ in man (Sheehan, 1941). The exact boundaries of this outflow differ * in the lower animals as will be seen from the following table:

TABLE I. *Usual arrangement of thoraco-lumbar and sacral outflows in man and common laboratory animals* (Sheehan, 1941)

	THORACO-LUMBAR OUTFLOW	SACRAL OUTFLOW
Man	T ₁ — L ₂	S ₃ + S ₄
Monkey	T ₁ or T ₂ — L ₃ or L ₄	S ₁ + S ₂ + S ₃
Dog	T ₁ or T ₂ — L ₄	S ₁ + S ₂ + S ₃
Cat	T ₁ or T ₂ — L ₄	S ₁ + S ₂ + S ₃
Rabbit	T ₁ — L ₅	S ₂ + S ₃ + S ₄

Preganglionic fibres which have travelled out along ventral roots leave the spinal nerve (not the ventral root as is generally depicted, fig. 52) at a point usually *distal* to the junction of the grey ramus with the spinal nerve. The bundle of fibres leaving each spinal nerve passes to the corresponding segmental vertebral ganglion, and, on account of the myelinated character of the fibres, such a nerve is called the *white ramus communicans*. It is important to remember that the white rami are *restricted* to the thoracolumbar region.

Each fibre of the white ramus on entering the corresponding segmental ganglion

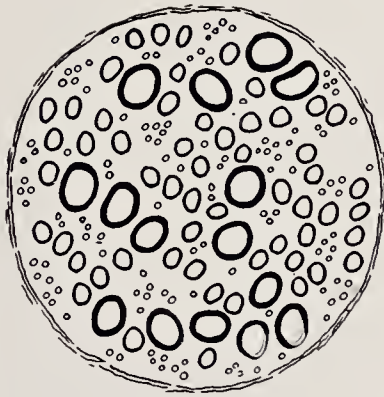
* The differences are significant since most of the early experimental work has been carried out in cat and dog, and the anatomical conclusions transferred erroneously to man. The cat and dog usually possess 8 cervical, 13 thoracic, 7 lumbar and 3 sacral spinal nerves; the monkey, 8 cervical, 12 thoracic, 7 lumbar and 3 sacral. Gaskell, however, counted 15 thoracic nerves in the dog in order that the subsequent lumbar and upper sacral nerves in man and dog might have the same enumeration. Thus he gave as the lower limit of the thoraco-lumbar outflow in the dog, the 25th spinal nerve which he called L₂, instead of L₄ as it should have been designated. The change in nomenclature passed unnoticed by many subsequent writers, and a confusion in description has existed ever since.

divides and gives off several collaterals, which terminate in synaptic relationship * with cells lying in one of the vertebral or prevertebral ganglia. Some end in the corresponding segmental ganglion of the vertebral chain. Others turn upwards to end in a segmental ganglion higher in the vertebral chain, or downwards to end in a segmental ganglion placed more caudally. The isolated segmental ganglia thus become linked together to form the sympathetic chain. Others pass through the vertebral chain into the splanchnic nerves to end in prevertebral ganglia (coeliac, superior and inferior mesenteric, etc.). The actual site of the synapse varies with different sympathetic functions. The preganglionic sympathetic fibres controlling the pupils, for example, terminate for the most part in the superior cervical ganglion, whereas those controlling the temperature of the face end in the inferior cervical ganglion. Finally, some preganglionic fibres pass directly through the vertebral chain and splanchnic nerves to end in the adrenal medulla. The latter is the *only* organ directly innervated by preganglionic fibres. The adrenal medulla contains numbers of ganglion cells, some of which were thought to be cell bodies of short postganglionic neurons interposed in the pathway, but the recent work of Hollinshead (1936) and Swinyard (1937) has confirmed the fact that preganglionic fibres come directly into relation with the chromaffin cells of the adrenal medulla. The latter, developed from the same source as the sympathetic ganglia, are homologous with the postganglionic neurons.

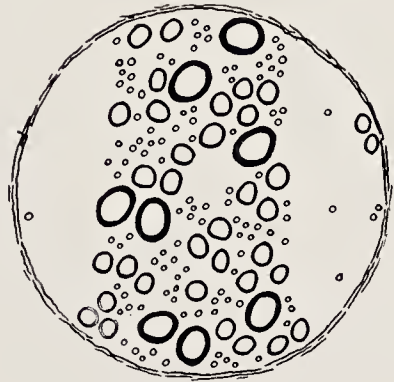
Postganglionic fibres start from cells in *any* of the vertebral and prevertebral ganglia and reach their destination (smooth or cardiac muscle or gland), either along blood vessels, forming a perivascular network, or along spinal nerves. Those going to thoracic and abdominal viscera travel with the artery supplying the particular organ. As they leave the vertebral chain they form bundles running medially towards the aorta and its branches, and constitute the visceral or splanchnic nerves. Postganglionic fibres going to the head, limbs and body wall, on the other hand, travel along spinal or cranial nerves. As they leave the vertebral chain they form bundles which join the spinal nerves. Since the fibres are for the most part (though not entirely non-medullated these bundles are termed *grey rami communicantes*. It is important to remember that grey rami pass to *every* spinal nerve, and are not restricted like the white rami to the thoracolumbar region. It is probable that all smooth muscle and most if not all the glands of the body receive sympathetic innervation.

From the histological studies of Sheehan and Pick (1943), the rami communicantes in man and monkey fall into four characteristic types (fig. 53). Type 1 (the white ramus) is filled with myelinated fibres of *all* sizes distributed irregularly throughout the nerve. The fine myelinated fibres, 3μ and under in diameter, are generally considered to be preganglionic, the rest afferent in nature. Types 2A and 2B (grey rami) are composed of non-medullated fibres with an occasional group of about a dozen large medullated fibres and a variable number of fine myelinated fibres, under 3μ in diameter, scattered uniformly throughout the nerve. In Type 2B these fine myelinated fibres may number several hundreds and curiously this

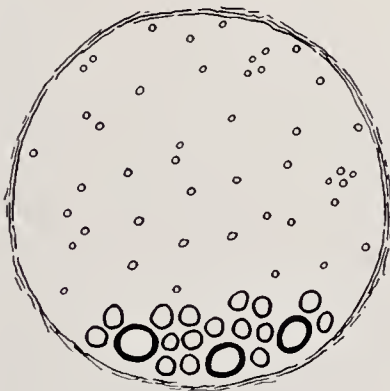
* The microscopical appearances of sympathetic synapses in normal, degenerating, and regenerating phases, have been studied by Gibson (1940). *Boutons terminaux* and *boutons de passage* can be seen, similar to those existing in the central nervous system but their number and size are surprisingly small. The largest number of boutons of whatever type seen on one cell and its processes was thirteen; compare this with the hundreds counted on one ventral horn cell in the spinal cord. The difference may be due to difficulties in staining technique, but there are other synaptic structures (pericellular nets, etc.) within sympathetic ganglia.



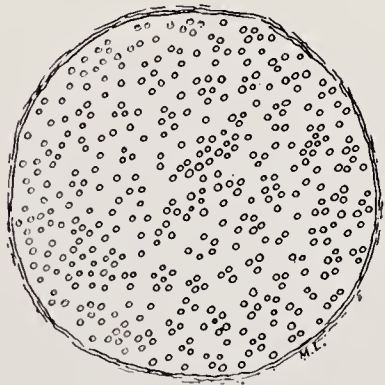
Type 1.



Type 3.



Type 2a.



Type 2b.

FIG. 53. Diagram illustrating types of rami of the monkey in accordance with their myelinated fibre components (Sheehan and Pick, *J. Anat.*, 1943, 77, 134).

type is found predominantly in the rami of the lower cervical and lower lumbar regions, *i.e.*, above and below the thoracolumbar level. Some of these fine medullated fibres are postganglionic and others probably afferent, which would indicate that the white rami are not the only portals of entry for the visceral afferents, as has hitherto been supposed. Type 3 is a truly mixed ramus, with areas of Type 1 and Type 2a in the same nerve bundle, and not merely white and grey rami running parallel.

The upper three or four cervical nerves are joined by grey rami from the superior cervical ganglion. The lower cervical nerves each receive one or more *superficial* rami from the middle or inferior cervical ganglia and a *deep* ramus from the inferior cervical ganglion via the vertebral canal. Small somatic branches from the cervical spinal nerves run to the prevertebral muscles along the cervical sympathetic rami, particularly those of C7 and C8, giving the latter a false appearance of a white ramus. This probably accounts for the occasional reports in the literature

of an upward extension of the thoracolumbar outflow to C8. The type fixation of the brachial plexus does not appear to be significant in this connection. In the thoracic region mixed rami are common, and there is often only one to each spinal nerve. The first thoracic nerve, however, is always joined by several rami and the most *distally* placed is usually the white ramus, which is the reverse of that depicted in most diagrams. In the lower thoracic and upper lumbar regions, each nerve is joined by one or more *oblique* (white) rami from the ganglion above, and one or more *transverse* (grey) rami from the ganglion below (Botar, 1932). The lower lumbar and sacral nerves customarily receive only one ramus each. The frequency of small ganglionic masses along the course of the sympathetic rami is much commoner than is generally supposed (Wrete, 1934).

The general plan of the sympathetic system can be best illustrated by one of Langley's experiments. If any ventral root (white ramus) is stimulated — the sixth thoracic, for example, — pilomotor responses occur over a wide area innervated by several dermatomes. Stimulation of the grey ramus to the sixth thoracic nerve, on the other hand, causes a band of pilo-erection corresponding to the dermatome innervated by that nerve.

PARASYMPATHETIC (CRANIOSACRAL) OUTFLOW: The same general arrangement holds, of preganglionic and postganglionic fibres, but the synapse is *close to or within the organ of supply*. On account of the restricted outflow and the long preganglionic fibres, not all smooth muscle receives a parasympathetic innervation (the nictitating membrane, the pilomotor muscles, probably the uterus, and the blood vessels of the limbs and trunk are probably supplied only with sympathetic nerves). The parasympathetic system has four primary levels of outflow:

1. *Hypothalamic outflow:* Preganglionic fibres from supraoptic and other nuclei of the anterior hypothalamus pass via the pituitary stalk to the neurohypophysis to innervate secretory cells (modified postganglionic neurons, see ch. XIII).

2. *Tectal outflow:* Preganglionic fibres, from cells of the Edinger-Westphal nucleus in the midbrain, travel with the third cranial nerve as far as the orbit, where they leave it and form synapses in the *ciliary ganglion*. Postganglionic fibres arising in the ciliary ganglion pierce the back of the eyeball (ciliary nerves) and terminate in the smooth muscle of the ciliary body, and in the constrictor pupillae.

3. *Bulbar outflow:* (i) Preganglionic fibres, arising in the superior salivary nucleus of the hindbrain, emerge as the *pars intermedia* which joins the ninth cranial nerve. Some of the fibres, leaving the ninth nerve as it lies in the tympanum, run forwards to end in the *sphenopalatine ganglion*, from which postganglionic fibres pass to the lacrymal gland. Others constituting the *chorda tympani* leave the ninth nerve after it has left the tympanum, and join the lingual nerve to reach the *submaxillary ganglion*. From here postganglionic fibres run to the submaxillary and sublingual glands.

- (ii) Preganglionic fibres, arising in the inferior salivary nucleus of the hindbrain, leave the medulla with the ninth nerve, and come into synaptic relationship with cells in the *otic ganglion*, from which postganglionic fibres pass via the auriculo-temporal nerve to the parotid gland.

- (iii) Preganglionic fibres, arising in the dorsal vagal nucleus, leave the medulla in the ninth, tenth and accessory part of the ninth cranial nerves. They constitute the major portion of the vagus nerve in the neck and through it reach the heart, bronchial tree, and gastrointestinal tract, as far down as the transverse colon. The synaptic junctions for the most part lie within the organ of supply, in the wall of the auricles and in ganglia of the myenteric and submucosal plexuses in the gut wall.

4. *Sacral outflow*: Preganglionic fibres arising from cells of the lateral grey matter pass out of the spinal cord in ventral roots of S3 and S4(S2 and S5 occasionally participating). They leave the corresponding spinal nerves, and run forwards as separate nerve bundles(pelvic nerves or *nervi erigentes*)on each side of the rectum. They form synaptic connections with cells in ganglia of the pelvic plexuses or within the walls of the rectum and bladder, from which postganglionic fibres arise to supply the hind-gut, bladder, and blood vessels of the generative organs.

The vasodilator mechanism through dorsal spinal roots, discussed in chapter II, is sometimes considered part of the parasympathetic outflow, but until the identity of the fibres concerned has been determined, and the significance of the mechanism in the intact animal established, this seems unwise. The fact that deafferentation of a limb has little, if any, effect on its vascular bed casts doubt on any tonic vasodilator influence via dorsal roots(Ascroft, 1937; Hinsey and Phillips, 1938). Convincing anatomical evidence of emerging fibres in dorsal spinal roots is lacking.

VISCERAL AFFERENTS: Since Langley's time it has been customary to restrict the term autonomic nervous system to efferent neurons only. Both sympathetic and parasympathetic nerves, however, contain many afferent fibres. Anatomically they are generally believed to be identical with somatic afferent neurons, their cell bodies lying in dorsal root ganglia, the central processes entering the cord, and the peripheral processes running via autonomic nerves to receptors within visceral structures(smooth and cardiac muscle and glands). Some of these, particularly those within sympathetic nerves, are sensory and are concerned in the production of visceral pain; others such as the afferent fibres in the vagus take part in specific reflexes, the aortic, carotid sinus, vasomotor, visceromotor, etc., all of which take place through the spinal cord and brain stem. There is some evidence that true reflexes can occur through peripheral ganglia whose connections with the central nervous system have been severed(Schwartz, 1934; Kuntz, 1940)which would mean that the cell bodies of certain visceral afferents may lie peripherally and their processes form synaptic connections directly with postganglionic neurons in sympathetic ganglia. Recent attempts with unquestionably decentralized ganglia have, however, failed to corroborate this evidence.

Clinically, from the standpoint of interrupting pain pathways, a detailed anatomy of the visceral afferent fibres is becoming increasingly important. Their pathways and portals of entry into the cerebrospinal axis are still too vaguely understood. It cannot be assumed that they always enter the cord at the same levels from which the corresponding efferent fibres emerge, for it appears likely that some of them enter via grey rami. A difference in threshold stimulation seemed to establish a physiological distinction between visceral and somatic afferents. It had long been observed that the abdominal and thoracic viscera, exposed under local anaesthesia of the anterior abdominal wall, could be pinched, cut and burned without the patient experiencing any pain whatever. Clinically the accurately localized, sharp pain of the skin in response to pricking or cutting was contrasted with the diffuse, vaguely localized pain of intestinal and gastric colic, with its peculiarly unbearable quality in its severest form. Any such fundamental difference between the two systems of afferents has been questioned by the recent studies of Lewis and Kellgren(1939), who find that the pain from muscle and deep ligaments, produced by injections of hypertonic saline, is diffuse, difficult to localize and gives rise to referred phenomena identical with those associated with visceral disease in man. The degree of localization in their opinion depends on the depth at which

the structure lies rather than on its nature. Furthermore it is well established now that inflamed viscera are sensitive to prick and to forms of mechanical stimulation which evoke pain from the skin (Wolf and Wolff, 1942), so the threshold difference may be only one of degree.

Morley's theory that in abdominal disease *referred pain* localized sharply at a distant point is derived not from visceral but from parietal peritoneum is still acceptable. It is best illustrated by the shoulder tip pain felt when the central portion of the under surface of the diaphragm is stimulated. The afferent nerve involved is the phrenic, and the peritoneum irritated is parietal. The pain is still felt in the shoulder after bilateral excision of the sympathetic chains from above the superior cervical ganglion as far down as the seventh thoracic (Hinsey and Phillips, 1940). The reference of pain is therefore not due to viscerocutaneous reflexes through sympathetic pathways as had been suggested. Reference of pain is clearly a *central nervous mechanism* and depends upon the fact that "both somatic and visceral afferent fibres carry impulses which affect a common pool of secondary neurones, and that the principles of summation and inhibition are applicable" (Hinsey and Phillips, 1940). The importance in clinical diagnosis of a clear understanding of the mechanism of referred pain will be found in the monographs by Morley (1931) and Jones (1938).

SYMPATHETIC AND PARASYMPATHETIC EXCITATION

The principal effects of sympathetic and parasympathetic excitation in particular parts of the body may be now briefly described. It is not possible in the space available to discuss the details of innervation of each visceral organ. For such information the student should consult the texts by Müller (1931) or Kuntz (1934). Here certain regions have been selected, where clinical application is more immediate, and where in the search for methods of alleviating symptoms, much of the underlying physiology and anatomy has been uncovered. The clinical applications of autonomic innervation are fully dealt with in the monographs by Livingston (1935) and White and Smithwick (1941).

One must bear in mind that, apart from species differences, which are considerable, the effects of sympathetic and parasympathetic excitation *vary according to the physiological state of the tissue at the time of experiment*. Thus in the cat, the effect of vagal stimulation on the stomach is increased peristalsis if the tonus of the organ is low at the time of stimulation, and relaxation (McSwiney and Robson, 1931). Obviously every reaction of an organism or of its parts, to a new stimulus, is superimposed upon a fluctuating base line of activity, which is a reflection of the organism's response to an ever changing environment. If these fluctuations are small in comparison to the artificially produced response, as they are in skeletal muscle, then the relation of the experimental observations to the particular stimulus can be more readily deduced. If, how-

ever, as in smooth muscle, the experimentally produced responses are superimposed upon a widely fluctuating base line, interpretation is considerably more difficult, and not always possible. Furthermore many nerves contain both motor and inhibitory fibres to the same organ. The effect of stimulation of the hypogastric nerve in the monkey, for example, is an initial excitation followed by a period of inhibition of all activity, and the two responses can be separated by nicotine, which in suitable doses blocks the excitatory response but leaves the inhibitory phase intact (Sheehan and Labate, 1942). A final complicating factor is added to the picture by anatomical connections which take place between sympathetic and parasympathetic nerves, particularly between the cervical sympathetic, the vagus and the phrenic nerves in the neck.

With these qualifications, and bearing in mind that autonomic regulation in the intact animal takes place through *reflex mechanisms, dependent upon afferent stimulation and integration at higher levels of the central nervous system*, we can proceed to a study of the effects of nerve excitation and section in specific organs.

Eye. Sympathetic preganglionic fibres leave the spinal cord in the upper two or three thoracic ventral roots and run upwards in the cervical sympathetic trunk to end in the superior cervical ganglion. Postganglionic fibres arising from cells in this ganglion travel along the internal carotid artery, and its branch the ophthalmic, to the orbit, where they innervate the blood vessels of eyeball, including those of the retina, the dilator pupillae, the smooth muscle in the upper eyelid, and, in lower animals, the smooth muscle at the back of the eyeball (Müller's orbital muscle) and the nictitating membrane. Stimulation of the cervical sympathetic nerve produces vasoconstriction of the orbital blood vessels, dilatation of the pupil, some elevation of the eyelid (hence widening of the palpebral fissure), and in lower animals a slight forward protrusion of the eyeball (proptosis) and retraction of the nictitating membrane.

Exophthalmos, which is a marked degree of proptosis, is of such widespread clinical interest that a more detailed statement concerning its mechanism is desirable. An excellent summary from which the following has been taken, has been given by Friedgood (1941).

Müller's orbital muscle is a mass of smooth muscle fibres close to the periosteal lining of the orbital cavity in the region of the inferior orbital fissure. It spreads in a thin layer over the orbital floor and anteriorly is continuous with the orbital expansion of the inferior oblique muscle. Posteriorly it can be followed to the lower extremity of the superior orbital fissure and even up to the wall of the cavernous sinus. The orbital muscle is a vestigial structure in man and therefore shows much

variation in size. Other smooth muscle fibres are found in the capsule of Tenon, an envelope of thin connective and elastic tissue in which the eyeball is slung. These fibres surround the anterior half of the eyeball in the form of an incomplete ring, and anteriorly extend into the eyelids, forming the superior and inferior involuntary palpebral muscles. The superior is the better developed of the two.

Müller reported that stimulation of the cervical sympathetic trunk caused protrusion of the eyeball of mammals in which the orbital muscle is well developed. More recently, however, Essex and Corwin(1937), making use of the exophthalmometer, have shown that the eyeball recedes several mm. during anesthesia, and that stimulation of the cervical sympathetic restores the globe to its pre-anesthetic position. True exophthalmos, however, does not occur under these experimental conditions. Experiments of this kind in man have naturally been few. Wagner in 1860 reported two cases and Turner in 1862 one case in which the cervical sympathetic trunk was stimulated in the decapitated head of a condemned individual. Exophthalmos was not observed. In 1904 MacCallum and Dandy reported two cases with negative results obtained during anesthesia. This has been repeated with accurate measurements of the position of the eyeball by Friedgood, Cattell and Beetham(1928) in a selected group of 8 patients with hyperthyroidism but no exophthalmos. No significant measurable change in position of the eyeball occurred in any of the experiments. In man exophthalmos can develop in the presence of sympathetic paralysis(Brain, 1939; Pochin, 1939).

It would seem that sympathetic innervation of the peri-orbital smooth muscle is not significant in the production of clinical exophthalmos. The mechanism of its production, and the abruptness of its appearance on occasion, still require explanation. According to Whitnall(1932), the eyeball maintains its normal position by virtue of the tonicity of the extraocular muscles. Because of their respective origins and insertions, he regards the four recti as retractors of the eyeball and the two oblique as protractors, but he does not believe that these muscles are mechanically in a position to produce exophthalmos. Brunton(1940) has found that acetylcholine produces proptosis in dogs, after removal of the superior cervical sympathetic ganglion and suggests that it produces a relaxation of blood vessels, which, when distended with blood, push the eyeball forward.

Horner's syndrome. Paralysis of the cervical sympathetic trunk, by experimental section or disease, produces in the eye a characteristic picture, known clinically as *Horner's Syndrome*. The features are of course the reverse of sympathetic excitation. There is dilatation of the orbital blood vessels(conjunctival redness), constriction of the pupil(myosis), slight drooping of the upper lid(ptosis). In lower animals there is some enophthalmos and the nictitating membrane falls across the eye. Intraocular pressure may be moderately raised on account of the hyperaemia.

The steps by which the clinical syndrome was analyzed in physiological terms is one of the fascinating stories in medical literature(Fulton, 1929). In the sixties of the last century, one Frau Anna Brändli presented herself to the Swiss ophthalmologist J. F. Horner(1869) of Zurich. Several weeks after her confinement, she had developed drooping of her right upper eyelid to such an extent that the lid covered the upper edge of the pupil. The eye was sunken into the orbit and the

pupil, although markedly constricted, reacted to light in normal fashion. The right side of the face was red and warm and dry, while the other side was cold, pale and moist. A temperature difference of 5° was noted between the two cheeks.

A similar syndrome had been observed in animals many years earlier (see Sheehan, 1936) by Pourfour du Petit (1727), but its significance had largely been forgotten, despite the fact that Cruikshanks (1795), Arneemann (1797) and Reid (1838) noticed redness of the conjunctiva after section of the cervical sympathetic trunk. Dupuy (1816) and Brachet (1837) described the same "inflammation" of the conjunctiva and an elevation of skin temperature on the ipsilateral side of the face after extirpation of the superior cervical ganglion. Brachet came nearest to the present concept of vasomotor tonus when he remarked that the "inflammation" was not an excitatory effect but an atony or paralysis. Budge relates that du Petit made his first experiment in Namur in 1712, and later (in 1725) repeated it before Winslow, Senac and Hunant in Paris. Du Petit had demonstrated myosis on section of the cervical sympathetic, but Buffi in 1846 was the first to show that stimulation of this nerve caused dilatation of the pupil. The experiment was repeated by Waller in Bonn, where Budge was then working; thus began in 1851 the collaboration of Waller and Budge on the innervation of the iris, which led to their account of the cilio-spinal centre in the lower cervical and upper thoracic regions of the cord, and of the course of the fibres in the cervical sympathetic. The next step was taken by Claude Bernard (1851) who found that on stimulating the cervical sympathetic trunk the opposite of what we now call Horner's syndrome was produced, *i.e.*, a widening of the palpebral fissure, dilatation of the pupils, constriction of the skin vessels, sweating of the skin, protrusion of the eyeballs forward in the sockets. (For details concerning fibres in cervical sympathetic chain, see Foley, 1943.)

The cervical sympathetic chain, in addition to the fibres to the eye, contains vasomotor, pilomotor and sudomotor fibres to the homolateral side of the face, and fibres to the lacrymal, salivary and sebaceous glands. The complete picture of paralysis of the cervical sympathetic trunk will include disturbances of these functions, the most obvious being vasodilatation and absence of thermoregulatory sweating on the same side of the face. They will be discussed below under separate headings.

Parasympathetic fibres from the tectal outflow reach the eye via the third nerve and ciliary ganglion (see above). They innervate the constrictor pupillae and the ciliary muscle, and form the efferent limbs of the light and accommodation reflex pathways. In the eye therefore, only the iris has with certainty a double innervation, and the sympathetic and parasympathetic effects are antagonistic, sympathetic excitation causing dilatation, parasympathetic constriction of the pupil. It exemplifies a principle of reciprocal innervation between the two systems which can be observed in many other organs. Constriction of the pupil in response to light is clearly a protective or conservative mechanism and is a discrete response in the eye. Dilatation of the pupil due to sympa-

thetic excitation is usually part of a more generalized sympathetic response of the body, but in accordance with the principle of reciprocal innervation, dilatation of the pupil can equally be caused by parasympathetic inhibition. The reflex dilatation of the pupil to painful stimuli from any part of the body is of this nature (Gellhorn, 1943).

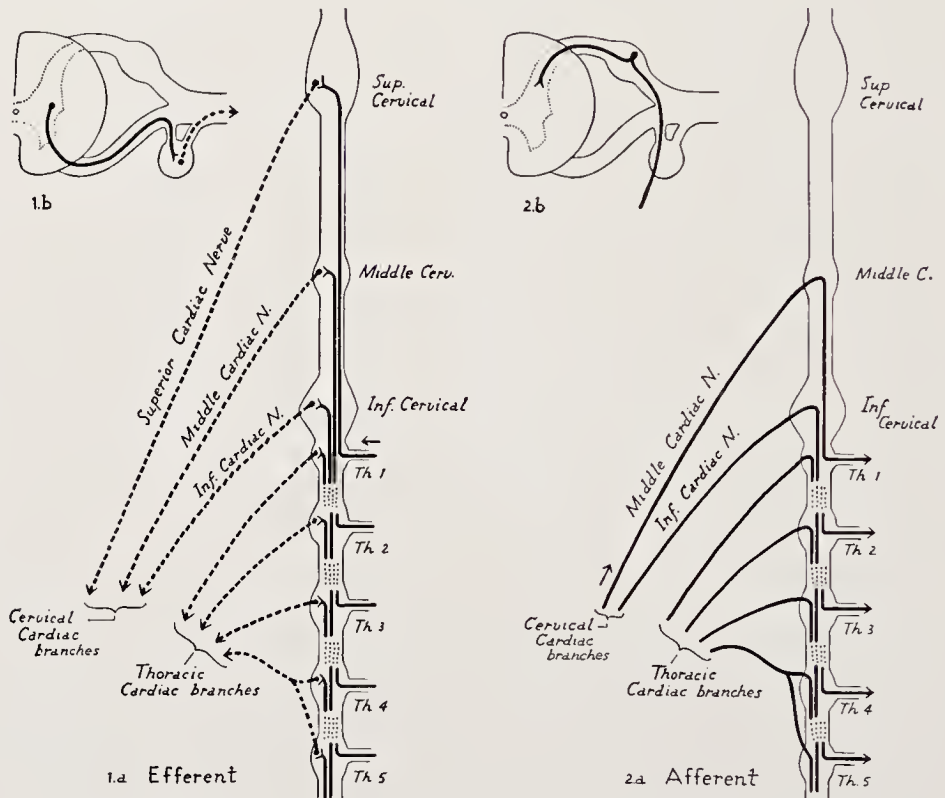


FIG. 54. Diagram of efferent (left) and afferent (right) sympathetic innervation of the heart. The sensory fibers from the myocardium travel for the most part with postganglionic fibers of the superior, middle and inferior cardiac nerves (Sheehan, unpublished).

Heart. Sympathetic preganglionic fibres pass via the ventral spinal roots of the upper 5 thoracic segments and enter via the white rami the corresponding upper thoracic ganglia (fig. 54). Some form synapses in these ganglia; others ascend to the inferior, middle and superior cervical ganglia. Postganglionic fibres from all of the cervical and the upper 5 thoracic ganglia run medially in separate bundles to converge on the cardiac plexus, and from thence reach the heart muscle along the coronary blood vessels. Parasympathetic preganglionic fibres come off the vagus in both the neck and upper part of the thorax, and converge like-

wise on the cardiac plexus and coronary vessels. Most of them end in synaptic relationship with cells in the ganglia of the cardiac plexus or within the walls of the auricles. Postganglionic fibres pass to the auricular muscle to the sinu-auricular node(chiefly right vagus)and to the auriculo-ventricular bundle(chiefly left vagus)and to the walls of the coronary vessels(Nonidez, 1939). According to Woollard(1926), the auricles and auriculo-ventricular bundle are supplied by both sympathetic and parasympathetic, but the ventricular muscle mainly by sympathetic fibres.

Both divisions of the autonomic innervation exert a tonic regulatory action on cardiac rate. The principle of reciprocal innervation holds; sympathetic excitation or parasympathetic inhibition causes cardiac acceleration; parasympathetic excitation or sympathetic inhibition causes cardiac slowing. The parasympathetic(vagal)innervation is probably dominant. In addition stimulation of the right vagus reduces the force of both auricular and ventricular systole, and stimulation of the left vagus by affecting conduction in the auriculo-ventricular bundle may bring about a condition of partial heart block. Stimulation of the sympathetic cardiac nerve on the right side is said to augment the force of auricular contraction, whereas stimulation on the left side is believed to increase the force of ventricular contraction(Fogelson, 1929).

Experiments on the innervation of the coronary vessels have given conflicting results, but the weight of evidence suggests that sympathetic activity dilates the coronaries, which would be in keeping with the needs of the accelerated heart. Katz and Jochim(1939), however, have recently brought forward evidence that sympathetic innervation contains in addition some dilators and the vagi only dilators to the coronaries.

Afferent fibres run in both the sympathetic and parasympathetic cardiac nerves. Those of the sympathetic are chiefly found in the *thoracic* cardiac branches and are apparently absent from the superior cervical cardiac nerve(fig. 54). The sympathetic thoracic cardiac nerves were not recognized until quite recently. Their importance has become evident since it was found that relief of cardiac pain in angina pectoris follows their anesthetization by paravertebral injection or their removal by upper thoracic sympathectomy(see White and Smithwick, 1941).

The afferent fibres in the vagus are probably non-sensory and are

concerned largely with cardiac and vascular reflexes (aortic, carotid sinus, Bainbridge, etc.). They are responsive to pressure changes in the circulatory system and chemical alterations in the blood. Bronk (1931) recorded from the carotid sinus nerve a burst of impulses followed by an interval of relative inactivity with each cardiac cycle. If the blood pressure is raised the discharge becomes continuous. In certain individuals the carotid sinus is hyperactive and slight pressure applied to the side of the neck may lead to sudden slowing of the heart and convulsive seizures. In these patients attempts have been made to denervate the sinus either by stripping its adventitial coat or dividing the carotid sinus nerve.

General vasomotor activity. The blood vessels, particularly the arterioles of the skin and skeletal muscles, are innervated solely by the sympathetic division, if we except the ill-defined vasodilator mechanism of dorsal roots. The coronary and pulmonary and probably also the cerebral and splanchnic vessels receive an additional innervation from the parasympathetic division. Regulation of the *coronary* circulation has already been mentioned. The sympathetic control of the *pulmonary*, *cerebral* and *splanchnic* vessels is in the same general direction as that of other blood vessels, *i.e.*, constrictor; the parasympathetic innervation is usually dilator. Certainly the cerebral (Forbes and Cobb, 1938) and pulmonary (Daly, *et al.*, 1940) vessels are not under the same degree of nervous control as are the blood vessels elsewhere, and it is doubtful if there is any tonic control of the splanchnic vessels, at least in a normal individual at rest in the supine position. On tilting the person from the horizontal position, however, reflex vasoconstriction comes into play serving to maintain arterial pressure at normal levels. This reflex response to change in posture is absent in subjects after high spinal anesthesia (Smith, 1940).

The *vessels* of the skin are clearly under tonic nervous control, for removal of the sympathetic fibres results in immediate vasodilatation and a consequent rise in skin temperature (fig. 55). Sympathetic excitation on the other hand produces blanching of the skin and a fall in surface temperature. Although sympathetic vasodilator fibres to the skin, more to the proximal than to the distal parts of a limb, have clearly been demonstrated (Lewis and Pickering, 1931; Burn, 1932; Fatherree and Allen, 1938; Grant and Holling, 1937), nevertheless the predominant sympathetic response in the skin vessels is one of *vasoconstriction*. Reflex peripheral vasoconstriction will occur in normally innervated extremities particularly in the fingers and toes in response to many forms of

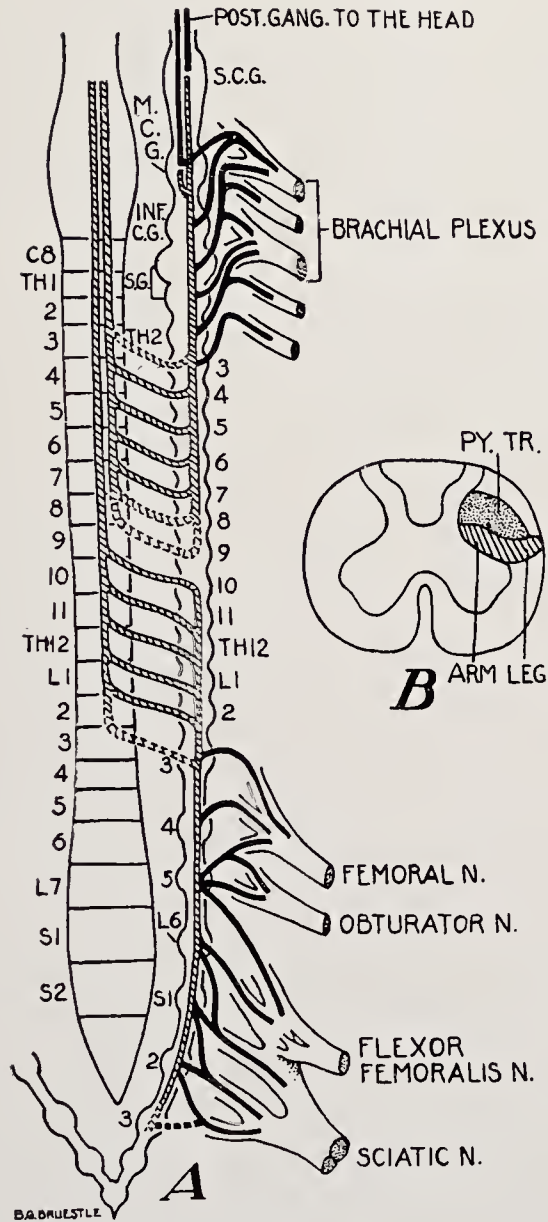


FIG. 55. A, Diagrammatic representation of outflow from spinal cord of preganglionic fibers (hatched) and postganglionic fibers (heavy black) for vasomotor supply of upper and lower extremities of macaque. Broken lines indicate inconstant fibers. SCG, superior cervical ganglion, MCG, middle cervical ganglion, INF.C.G., inferior cervical ganglion, SG, stellate ganglion, Th2, second thoracic ganglion, L1, first lumbar ganglion, S1, first sacral ganglion. B, Diagram showing position of vasomotor pathways in spinal cord (Ascroft, *Brit. J. Surg.*, 1937, 24, 792).

stimulation, to changes in arterial pressure(aortic and carotid sinus reflexes), to cold, pain, a sudden noise or even a deep breath. These reflexes do not occur in a sympathectomized area. This fact has been taken into consideration in the treatment of vasospastic states, and sympathectomy has proved its value in relieving the spasm of Raynaud's syndrome(an exaggeration of the normal response in the fingers to cold).

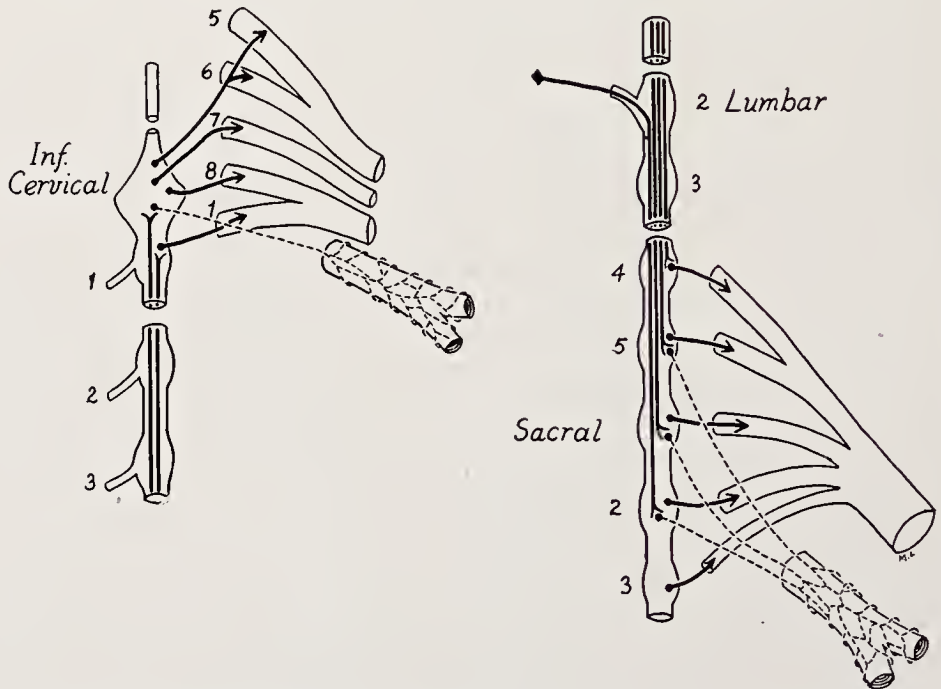


FIG. 56. Diagram of innervation of blood vessels of limbs. The level of incision for postganglionic stellate ganglionectomy(Smithwick operation)is compared with the preganglionic procedure for lumbar sympathectomy. (After Sheehan, unpublished.)

Recurrence of symptoms frequently followed sympathetic denervation of the arm for Raynaud's syndrome. Lewis(1937b)has established that early relapses (within a few days of operation)must be due to some "local fault" in the digital vessels which is sufficiently severe to nullify the effectiveness of the vasodilatation obtained by sympathetic denervation. Late relapses which do not show symptoms for several months after operation cannot be accounted for by increased sensitivity of the denervated blood vessels to circulating adrenalin, for this hypersensitivity is maximum eight to ten days after denervation and is perhaps less evident when clinical relapse becomes apparent. Many of these late relapses were shown to be due to regeneration of vasoconstrictor fibres(Simmons and Sheehan, 1939). The rapidity of anatomical regeneration and functional recovery within the autonomic nervous system has been well known since Langley first demonstrated its occurrence. In the cat divided preganglionic fibres established functional regeneration in the fore limb in 36-61 days(Hinsey, Hare and Phillips, 1939). After section of the cervical sympathetic chain below the superior cervical ganglion, Gibson(1940)

found the first signs of regeneration in 11 days and reappearance of boutons 44 days after operation, when restoration of function in the ganglion returned.

Smithwick's operation (1936) for the sympathetic denervation of the upper limb was designed to affect a preganglionic section and at the same time to prevent regeneration, and it has proved successful (fig. 56). In the monkey the sympathetic preganglionic outflow to the upper extremity extends from T₄ to T₈, inclusive, and to the lower extremity from T₁₂ to L₃, inclusive (Sheehan and Marrazzi, 1941). These levels are in close accordance with Foerster's findings in man (1939), but Smithwick believes that T₂ and T₃ may sometimes contribute preganglionic fibres to the arm in man. It is highly unlikely that T₁ makes any contribution to the sympathetic innervation of the upper extremity. The postganglionic cells related to the arm, following Langley's analysis in the cat, are generally believed to be in the inferior cervical and first thoracic ganglia, and possibly extending down as far as the second thoracic. Livingston (1932) advanced arguments in favour of still further downward extension, to the ganglia of the third and fourth thoracic segments, and in 1932 recommended removal of the third ganglion alone, or the second and third, as preferable to the cervicothoracic ganglionectomy commonly practiced at that time. The operation was first performed June 1931 by Livingston. Subsequently Telford (1935) and Smithwick (1936) advocated a similar approach, but designing their operations with the intention of leaving postganglionic cells intact, for the greater sensitivity of completely denervated vessels to adrenalin had been convincingly demonstrated by Smithwick, Freeman and White (1934). In the lower extremity it seems likely that the synapses of the sympathetic nerve fibres are situated in the ganglia from the third lumbar to the third sacral.

Postganglionic nerves to the limbs take one of two pathways (Todd, 1912; Woollard, 1926). Some join the main limb vessel (subclavian or iliac) forming a perivascular network in the adventitia, but probably not reaching any considerable distance into the limb. Others pass through the grey rami into the nerves of the limb plexuses, which they accompany into the hand and foot, where they are distributed to the distal branches of the vascular tree (fig. 56). It is difficult to see therefore how a perivascular sympathectomy, stripping the adventitial coat of the main limb vessel over a short distance, as advocated by Leriche (1937), can be effective as a method of denervation. Nevertheless the operation has been found useful in certain instances and we are forced to admit that our present knowledge of the course of the efferent and afferent nerves accompanying blood vessels is still inadequate. Apart from the questionable vasodilator mechanism along dorsal roots, *no para-sympathetic fibres reach the limbs or body wall.*

Vasomotor reflexes of both constrictor and dilator nature occur in *skeletal* muscle in response to adrenalin and carotid sinus impulses, and no doubt play a role, with vasomotor reflexes in the skin and splanchnic bed, in the maintenance of an adequate blood pressure. Sympathectomy does not alter the hyperaemia of skeletal muscle which accompanies exercise, a mechanism which is probably associated with release of a vasodilator substance from the active muscle fibres.

Shifts in circulating blood from the *splanchnic bed* occur during muscular exercise and after severe haemorrhage. This splanchnic vasoconstriction is largely a function of the sympathetic nerves. The spleen and

liver participate. The spleen by contraction of its own musculature can be reduced to one third of its size during muscular exercise. Contraction of the liver is due mainly to constriction of the portal vessels. Although the splanchnic vascular bed is probably not under the same tonic vasomotor control as are the skin vessels, the effects of vasomotor reflexes are obvious in this region. In addition to massive shifts of blood volume as occur in major emergencies, smaller fluctuations in circulation through abdominal viscera can be detected under mild emotional stress. The renal blood flow, as measured by diodrast and inulin clearance tests, dropped in one individual when exposed to a situation invoking fear (Homer Smith, 1939). Ever since it was proved experimentally by Goldblatt, *et al.* (1934), that partial and sustained occlusion of the renal arteries in dogs will lead to hypertension, attempts have been made to alleviate the clinical state of essential hypertension by sympathetic denervation. Renal blood flow in such patients is apparently little altered by such sympathectomy (Corcoran and Page, 1941), but in selected cases Smithwick has obtained very encouraging results, particularly in the relief of subjective complaints. Smithwick's operation is not merely a renal denervation; it removes sympathetic control over a wide area of the splanchnic vascular bed.

The nervous control of *veins* and of the arteriovenous anastomoses in the skin is apparently similar in nature to, but less marked in degree than, that of arteries (Franklin, 1937, ch. x). *Capillaries* possess contractility independent of changes in the arterioles, and in many areas of the body they contract on sympathetic excitation. Stöhr (1935) has observed unmyelinated nerve endings passing to endothelial cells of skin vessels but the direct capillary innervation appears not to be widespread. Capillary permeability is altered following sympathectomy, but the direction of the change and its relation to calibre size have not yet been fully elucidated.

Sudomotor and pilomotor activity: Accompanying the vasomotor fibres to the skin are sympathetic postganglionic fibres which on excitation give rise to sweating and to contraction of the smooth muscle of the hair follicles, causing erection of hair. Although sweating commonly accompanies peripheral vasodilatation as a mechanism of heat loss, it is independent of vasomotor changes. It can occur in association with vasoconstriction, as in the cold clammy hand of fear, and it does not necessarily follow peripheral vasodilatation, *viz.*, the hot dry skin of

fever. Sweating occurs reflexly in response to increased heat (environmental or during muscular exercise) and to emotion. In both instances it is abolished by sympathetic denervation. Thermoregulatory and emotional sweating are not identical in distribution. The latter is more localized to the palmar surfaces of the hands and fingers, the plantar surfaces of the foot and toes, the axilla and the forehead. A gustatory reflex sweating (produced by eating spicy foods) is confined to the face, the upper lip and tip of the nose (List and Peet, 1938). Hyperhydrosis on an emotional basis can be effectively treated by sympathectomy (White, 1939), but the area of anhydrosis so produced is often accompanied by hyperhydrosis elsewhere, apparently a compensatory phenomenon, which disappears on the return of normal sweat secretion if regeneration of sympathetic fibres occurs.

Absence of reflex sweating, together with vasodilatation, in the affected area follows peripheral nerve paralysis and the line of demarcation of sudomotor and vasomotor changes follows closely the boundaries of the area of sensory loss (Guttman, 1940). Indeed an ulnar nerve paralysis can often be spotted by running the forefinger over the patient's palm from ulnar to radial side. Increased resistance to the examining finger on account of moisture is at once encountered on leaving the ulnar distribution. Clearly the sudomotor, vasomotor and pilomotor fibres are distributed by the cutaneous nerve to the same skin area as the sensory fibres.

It had long been observed that injection of adrenalin produced vasoconstriction and erection of hair without any sweating, whereas pilocarpine and acetylcholine induced sweating. The apparent paradox has now been explained for it has been shown that sudomotor sympathetic fibres, in contrast to vasomotor and pilomotor fibres, are cholinergic.

Sweating in response to pilocarpine and acetylcholine can still be induced after complete sympathetic denervation. This might be due to sensitivity to direct chemical stimulation, but List and Peet (1938) have observed that in man, all sweating in response to therapeutic doses of pilocarpine and acetylcholine is abolished by section of a peripheral mixed nerve, if time is allowed for degeneration of nerve fibres. It persists, however, if the peripheral nerve is merely blocked by novocaine. There may be here a link with the local vasodilator mechanism of sensory nerves, operating in the "flare" of the triple response to local irritation. A dilator substance (*e.g.*, acetylcholine) may be diffused from such fibres, and together with the injected acetylcholine or pilocarpine be sufficient to bring about a sudomotor response through direct action on neighbouring sweat glands. This would not necessitate the postulation of a double innervation of sweat glands, as suggested by List and Peet (1938), for which there is no anatomical evidence.

Interpretation of the pilomotor response is more obvious in lower animals. Erection of hair in the cat or of feathers in the bird produces a thick insulating coat against the cold. The completeness of a sympathectomy can be tested simply by

observing the animal's response to cold; if a ganglion has been missed a narrow band of hair will be erected in the corresponding area of distribution. In man the same reaction to cold results in the characteristic "goose-skin." There is probably also a more directly protective function in the phylogenetic development of the pilomotor response, for the erection of the porcupine's quills is of this nature.

Endocrines: Excitation of sympathetic preganglionic fibres which reach the *adrenal medulla* via the thoracic splanchnic nerves results in liberation into the blood stream of adrenalin(epinephrin), which accents the total sympathetic response. The two mechanisms are so closely interlocked that it is customary to speak of the sympathico-adrenal system. Adrenalin mimics everywhere the effects of sympathetic excitation, except for its few cholinergic elements. It also raises the blood sugar level, by depletion of glycogen stores, thus liberating potential sources of energy which may be required in a situation of emergency. Adrenalin also has a direct effect in reducing fatigue in skeletal muscle, possibly by increasing its irritability(Bülbring and Burn, 1942).

The anterior *pituitary*(adenohypophysis)receives sympathetic fibres via the carotid plexus. The synaptic connections are in the superior cervical and it receives a parasympathetic component from the Vidian ganglion(Zacharias, 1942). Phillips(see Hare and Hinsey, 1942)has recorded action potentials from the anterior lobe of the pituitary during stimulation of the cervical sympathetic trunk. Other fibres reach the pituitary directly from the hypothalamus via the supraopticohypophysial tract(ch. XIII).

A vasomotor innervation of the *thyroid gland* is well known, but there is at present no direct proof of a secretory innervation. The mild hypoactivity of the thyroid which follows bilateral cervical sympathectomy results from withdrawal of anterior pituitary innervation (thyrotropic hormone). A similar mechanism has been tentatively put forward by Friedgood and Cannon(1940)to explain signs of hyperthyroidism(increased basal metabolic rate, tachycardia, and unilateral exophthalmos)which occurred in 2 cats(out of 28)with an end-to-end anastomosis between the proximal end of the phrenic and the(upper) distal segment of the divided cervical sympathetic trunk. Resection of the anastomosis in one animal brought the metabolic rate down to the normal level. The results confirmed similar interesting observations by Cannon, Binger and Fitz(1915).

The effect of parasympathetic excitation on the *islets of Langerhans* is to stimulate the liberation of insulin, but the extent to which the islets

are normally under nervous control has not been established. The sympathico-adrenal system which raises the blood sugar level by depletion of glycogen storage is therefore counteracted by a vago-insulin system(Gellhorn, 1943).

Respiratory System: The autonomic innervation of the respiratory system exemplifies the close inter-relation between the somatic and autonomic spheres. Respiratory rate and amplitude is regulated from the respiratory centre in the medulla through somatic nerves(phrenic, intercostals, etc., ch. viii). The respiratory centre is sensitive to alterations in CO_2 and O_2 tension, but also to impulses reaching it along many afferent nerves, not the least of which are the afferent fibres in the vagus from various parts of the respiratory tract. The respiratory centre is also influenced by the aortic and carotid sinus reflexes. When the vagi are cut respiration becomes slower, irregular and deeper in amplitude. Thus the afferent fibres in the vagi exert a tonic influence on the respiratory centre. Increased rate and amplitude occur during times of emotional stress and diffuse sympathetic activity.

The smooth muscle of the bronchial tubes receives both a sympathetic and parasympathetic innervation(Elftman, 1943). The sympathetic fibres emerge from the cord in the upper 3 or 4 thoracic nerve and synapse in the inferior cervical and upper thoracic ganglia. Stimulation of the thoracic sympathetic chain produces bronchodilatation, an aid to the intake of air during times of emergency. The parasympathetic fibres are vagal and reach the bronchial tree from the anterior and posterior pulmonary plexuses. They exert a tonic constrictor action on the bronchial musculature, for section of the vagi is followed by bronchodilatation. Stimulation of the peripheral end of the cut vagus produces bronchial constriction, on both ipsilateral and contralateral sides. In the intact animal the effect can be brought about by reflexes originating from irritation of the mucous membrane of the upper respiratory passages. The parasympathetic innervation has therefore a protective quality, preventing the passage of foreign agents down the respiratory tract. In certain individuals with high sensitivity the protective reflex is exaggerated and bronchial spasm(asthma)may occur in response to various stimuli. Adrenalin will usually relieve the bronchial spasm in a dramatic manner, demonstrating once more the general antagonism in action of the two divisions of the autonomic nervous system.

Gastrointestinal tract: Sympathetic fibres reach the coeliac, superior

and inferior mesenteric plexuses via the thoracic and lumbar splanchnic nerves. From the ganglia in these plexuses postganglionic fibres arise and accompany the blood vessels to the various parts of the gastrointestinal tract. Parasympathetic fibres from the vagi (particularly the right) reaching the same plexuses pass through without synaptic transmission. They end around ganglion cells in the myenteric and submucosal plexuses in the gut wall. Hill (1927) who has made an extensive study of these cells describes two general types, Type 1 which from the arrangement of its axon she describes as associative, and Type 2 whose axon ends in relation to smooth muscle fibres and is clearly the vagal postganglionic neuron. The vagi supply the fore and midgut, *i.e.*, as far as the splenic flexure (approximately) and the sacral parasympathetic outflow supplies the hindgut (from splenic flexure to rectum) in like manner.

Both splanchnic and vagal nerves contain motor and inhibitory fibres and the effect of nerve stimulation varies according to the physiological state of the organ at the time of experiment. Broadly speaking, however, during sympathetic activity tonus and peristalsis are reduced and the sphincters closed throughout the entire gut. Digestive juices are generally reduced and mucus secretion abundant.* The processes of digestion are thereby inhibited and the emptying time greatly prolonged. Stimulation of any afferent nerve (*e.g.*, the central end of the sciatic) produces reflex inhibition of gastric and intestinal motility. Injury, particularly to the head, is frequently followed two to three days later by vomiting of undigested food partaken just before the accident. Parasympathetic activity, on the other hand, promotes digestion and aids in the passage of the food through the gut. Peristalsis is increased, the sphincters relaxed and the production of digestive juices, including salivary and pancreatic, is stimulated. Digestion, however, can proceed adequately following bilateral section of the vagi at the level of the diaphragm and bilateral section of the splanchnic nerves, and the preoperative level of tonus and peristaltic activity are soon reestablished.

Wolf and Wolff (1942) have recently made important studies in this connection on a patient with a large gastric fistula. Hyperaemia of the gastric mucosa accompanied increased motor activity and secretion.

* Stimulation of the cervical sympathetic trunk, however, produces a slight flow of thick saliva, and splanchnic stimulation causes some external pancreatic secretion (Babkin, *et al.*, 1939).

Such a state, manifesting parasympathetic activity, accompanied intake of food, discussion of appetizing dishes, and periods of emotional stress characterized by suppressed resentment and aggression. The feeling often described colloquially as a "wish to eat" the subject of resentment is strangely patterned by the condition of the stomach! If the emotion is accentuated small hemorrhagic erosions of the mucosa appeared (see discussion of hypothalamus in peptic ulceration in ch. XIII). Pallor of the mucosa, decreased gastric motility and secretion occurred at other times, more particularly when the patient was in a psychological state of fear (Flood, 1943) and the sympathetic system apparently dominant.

Imbalance between the two divisions is revealed in the clinical conditions of cardiospasm, pylorospasm and megacolon (Hirschsprung's disease), in all of which the sympathetic side dominates the picture. Hurst believes there is a failure of relaxation rather than a spasm of sphincters. Spinal anesthesia which blocks the thoracolumbar outflow may restore the condition to a normal balance. In megacolon Ross (1939) has offered the interesting suggestion that in certain individuals there may be developmentally an anatomical gap between the end of the vagus and the beginning of the sacral innervation to the large intestine, and that in this interval the sympathetic nerves provide the only extrinsic innervation.

In earlier clinical literature there was a tendency to classify patients as *sympathicotonic* or *vagotonic* individuals, according to the particular division of the autonomic nervous system which seemed to be predominant. The concept, though it contained an element of truth, is now discarded, for the same individual exhibits sympathetic and parasympathetic manifestations in different situations, and frequently *both are called into play at the same time in a selective manner*.

Reproductive organs: The sacral parasympathetic outflow to the reproductive organs is chiefly vasodilator, concerned with the engorgement of erectile tissue. The secretions of the prostate and vagina are increased. It is customary to regard the *uterus* as innervated by sympathetic nerve fibres only. Although gross anatomical preparations show fibres from the sacral outflow apparently entering the uterus and tubes, physiological studies on the whole do not confirm this. Increased activity in the uterus of the monkey has occasionally followed stimulation of the ventral roots of S₁, S₂ and S₃, but the responses may be indirectly the result of vaginal contractions. The effects of hypogastric nerve stimula-

tion vary according to the species, to the phase of the oestrus cycle, and to the presence or absence of pregnancy (Reynolds, 1939; Labate, 1941). Langley and Anderson (1895) were the first to show that hypogastric stimulation, normally inhibitory to the non-pregnant uterus of the cat, became excitatory during pregnancy. The same reversal follows the administration of preparations of ergot. In the rabbit and monkey hypogastric stimulation is always excitatory, though a subsequent inhibitory phase can usually be detected. These sympathetic excitatory fibres in the hypogastric nerve form synaptic connections with cells in ganglia of the pelvic plexuses, *i.e.*, close to the organ of supply, an exception to the general plan of the sympathetic system. It has been suspected that the postganglionic neurons may be cholinergic. Excision of the hypogastric plexus (presacral nerve) has been used in the treatment of primary dysmenorrhea. Its success may be due to interruption of excitatory fibres and so to diminished uterine activity or to division of sensory fibres which run in the hypogastric plexus.

Bladder (see ch. viii): The sympathetic innervation reaching the bladder via the hypogastric (presacral) nerve are distributed to the blood vessels and to the trigone, to Bell's muscles and to the crista urethrae. There is no convincing evidence that they innervate the longitudinal or circular coats of the bladder wall which are supplied exclusively by the sacral parasympathetic outflow. (Langworthy, Kolb and Lewis, 1940.) According to these authors, when the sympathetic supply is stimulated the ureteral orifices close and are pulled towards the midline; the base of the bladder moves downwards, carrying a portion of the mucosa towards the vesical orifice. The movement is slow and of small amplitude, not persisting if the stimulating current is continued for several seconds. There is also, in the male, contraction of the prostatic musculature and of the smooth muscle of the seminal vesicles and ejaculatory ducts. Section of the sympathetic nerves produces no appreciable modification of vesical activity. The closure of the "internal sphincter," seen by Learmonth (1931) on stimulating the hypogastric plexus in man, has been interpreted as supporting the widely accepted theory that the sympathetic fibres inhibit the vesical muscle and contract the "sphincters." Any action of the sympathetic fibres upon urethral resistance, however, acts according to Langworthy, *et al.* (1940), not at the vesical orifice but in the prostatic urethra, and has only a sexual function. The sympathetic fibres, he believes, have solely vasomotor and sexual functions in relation to the bladder and urethra. Langworthy's interpretation thus discards any antagonism between the sympathetic and parasympathetic innervations of the bladder, and it throws a new light on bladder symptoms in man, which have been quite erroneously referred to as "sphincter disturbances."

NEURO-EFFECTOR AND SYNAPTIC TRANSMISSION

Adrenalin, the active principle of the adrenal medulla was isolated in 1894 by Oliver and Schäfer. In 1904 Elliot showed that with minor modi-

fication its effect mimicked that of the sympathetic nervous system (see Cannon, 1934). Dale (1914) found that acetylcholine when injected into the blood stream reproduced the effects of parasympathetic excitation, and in 1921 Loewi demonstrated the presence of a cardio-inhibitory substance (vagus substance) in the perfusate from a frog's heart after vagus stimulation, and the presence of a cardio-accelerator substance after sympathetic stimulation. Final proof of the liberation of an adrenalin-like substance (*sympathin*) at most neuro-effector junctions of sympathetic postganglionic fibres was given by Cannon and Rosenblueth (1937), and of the liberation of acetylcholine at the neuro-effector junctions of parasympathetic postganglionic neurons by Dale and Feldberg (1933). The rapid breakdown of acetylcholine by cholinesterase which makes its recognition difficult in such experiments can be delayed by the eserine.

It became generally believed that the effects of nerve stimulation were brought about by the mediation of these chemical substances, and in 1933 Dale proposed the terms *adrenergic* and *cholinergic* to distinguish the two types of fibres. It was soon discovered that the innervation of the sweat glands and some of the vasodilator fibres of the sympathetic system were cholinergic. The terms "adrenergic" and "cholinergic" therefore do not correspond exactly to "sympathetic" and "parasympathetic," respectively. The latter is essentially an anatomical subdivision. "Sympathin" similarly has not quite the same connotation as adrenalin. Cannon and Rosenblueth (1937) suggested that adrenalin may be released at adrenergic nerve endings, but that it is modified in one of two ways at the effector, so that there ensues either a Sympathin E with excitatory action (as on blood vessels in the skin), or a Sympathin I with inhibitory effects (as on peristaltic activity of the gut).

Acetylcholine, one of the products of nerve metabolism, is liberated in relatively larger quantities at ganglionic synapses, whether they be sympathetic or parasympathetic. Addition of small doses of acetylcholine to the perfused ganglion will produce activity in the postganglionic neurons. It has been suggested therefore that synaptic transmission is also brought about through chemical mediation (Dale, 1937). For full discussion of synaptic transmission, see chapter iv).

That adrenalin exercises a specific inhibitory action on sympathetic synapses has been demonstrated by Marrazzi (1939, 1943). He suggests that this may constitute a self-limiting mechanism capable of checking the widespread activity produced by sympathico-adrenal discharge when this has reached a high level — an example of homeostatic regulation. Bülbring and Burn (1942) find, however, that the excitatory effect of acetylcholine at the ganglion is augmented by small doses, though depressed by large doses of adrenalin. The chromaffin tissue in all sympathetic ganglia and paraganglia must be borne in mind as a possible source of adrenalin. *Chromaffin tissue is widely distributed throughout the body.*

SENSITIZATION. Reference has already been made to the increased sensitivity of denervated smooth muscle to circulating adrenalin. It ap-

pears 8 to 10 days after postganglionic sympathectomy, presumably after degeneration of the nerve fibres, although it is also present to a less degree after preganglionic section. Denervated sweat glands become sensitized to acetylcholine. Degeneration of preganglionic fibres to the superior cervical ganglion results in increased sensitivity of the postganglionic neurons to the stimulating action of acetylcholine (Cannon and Rosenblueth, 1937). The principle appears to have wide application. The sensitization to chemical agents of all autonomic effectors and of nerve cells, both ganglionic and central, when partially or completely excluded from their normal nerve connections, has been formulated by Cannon (1939) into a *law of denervation*. The completely denervated nictitating membrane has been used extensively as an indicator of circulating adrenalin in the intact anesthetized animal (Hampel, 1935). Until recently it has been generally believed that while the sympathetic hormone, adrenalin, circulated freely in the blood acetylcholine, on account of its instability, does not ordinarily reach the blood stream. Bender (1938) has clearly shown, however, that acetylcholine may also gain access to the blood in detectable quantities during emotional states. During fright, the denervated muscles of the face in the monkey contract involuntarily, and similar activity can be evoked in these muscles by intravenous injection of acetylcholine. Both types of contraction are potentiated by eserine.

TOTAL SYMPATHECTOMY

When the activities of the sympathetic and parasympathetic systems are considered broadly, it becomes obvious that the two systems interact with one another in a manner designed to maintain constancy in the internal conditions of the body. Claude Bernard appreciated that animals became relatively independent of their external environment only after they, as warm-blooded animals, had evolved a mechanism for preserving the stability of their internal environment. He suspected, and Cannon proved, that the nervous system is in large measure responsible for maintaining "constant" conditions within the body. The sympathetic division is probably dominant in preserving homeostasis, but both sympathetic and parasympathetic responses are called into play, either simultaneously or sequentially, and the total response is the resultant balance between two opposing forces. Furthermore, although the sympathico-adrenal system has a tendency towards massive

discharge, one part may be affected without necessarily involving the whole.

It was obvious that interest should arise in the effects of total removal of one or both divisions of the autonomic nervous system. In Cannon's laboratory studies have been made on the responses of completely sympathectomized animals, in which the vertebral chains had been removed bilaterally from above the superior cervical ganglion down to the lower lumbar region. The entire thoracolumbar outflow of preganglionic fibres is thereby eliminated. Such animals can maintain their body temperature and blood pressure within normal limits, if kept in the protected surroundings which a laboratory offers, but they fail to do so when exposed to situations of undue stress requiring rapid adjustments, such as hemorrhage, oxygen want, hypoglycemia and cold. Cats are much more susceptible to such changes than are dogs, after complete sympathectomy (Hodes, 1939; McDonough, 1939). In such animals, fatigue due to muscular exercise appears early. On exposure to cold the cat shows no pilo-erection, but shivering comes on sooner and is more marked; the body temperature falls. Injection of insulin will throw the sympathectomized cat or dog into hypoglycemic convulsions, whereas in the normal animal the fall in blood sugar level invokes a profuse discharge of the sympatho-adrenal system and a consequent depletion of glycogen stores to restore the blood sugar to normal levels.

The fact that the totally sympathectomized animal can survive in a protected state of existence, that the essential processes of circulation, respiration, digestion and reproduction can proceed, does not indicate that the sympathetic system is normally inactive except in extreme emergency. The body has obviously other slower mechanisms of adjustment, chemical, hormonal, etc., but the autonomic nervous system is brought into play constantly with every motor act and with every phase of emotional behaviour.

ROLE IN EMOTIONAL BEHAVIOUR

That emotional behaviour is characterized by alterations in visceral and vascular activity has long been recognized. Blushing, weeping, tachycardia, a "sinking feeling in the pit of the stomach" and "nervous headache" (caused by cerebral vasodilatation) are familiar to everyone. The role of the sympathetic system in the motor expression of emotion, of fear and rage, has been emphasized by Cannon. The typical picture

of profuse sympathetic discharge, the dilated pupils, rapid heart, deepened respirations, pallor, sweating and dry mouth, is characteristic of the behaviour of a frightened individual. But parasympathetic responses are also observable during emotional behaviour. Secretion of gastric juice and hypermotility of the stomach accompany the sight and smell of appetizing food, only so long as the vagi are intact. The bladder and rectum may be emptied involuntarily during emotional stress, and the sacral parasympathetic outflow participates in sexual excitement. Wolff's patient with the large gastrostomy (mentioned earlier) showed hypermotility, hypersecretion and hyperaemia of the stomach during a psychological phase of "suppressed resentment," and recently Gellhorn, Cortell and Feldman (1941) have added the conclusive evidence that in the cat, confronted by a barking dog, there is a secretion of insulin which is abolished by vagotomy.

It is not justifiable to interpret types of emotional behaviour in terms of purely sympathetic or parasympathetic responses. Both systems are frequently activated simultaneously. Emotion is of course a conscious feeling in which the activities of the cerebral cortex are an integral part. The autonomic system is only *part* of the motor mechanism through which emotional states are *expressed*. The skeletal musculature participates equally, as evidenced by tremor, "tensing" of muscles, and facial twitching, and a totally sympathectomized animal can still exhibit emotion. The sham-rage reaction of a decorticate animal, with the hypothalamus intact, will be dealt with in the next chapter.

From the clinical standpoint it is important to realize that an autonomic response, which has been invoked in the interest of homeostatic balance or as an expression of emotional behaviour, may become excessive, and the functional disturbance, if sustained, may eventually lead to organic change. In the late stages of Raynaud's syndrome with repeated vasospasm in the hands in response to cold or emotional stress, ulcerations may appear in the tips of the fingers. More marked trophic changes, of a similar nature, occur in the state of causalgia described by Weir Mitchell. Haemorrhagic erosions in the gastric mucosa, associated with hypermotility and hypersecretion, may follow prolonged periods of emotional tension. Pathological changes therefore can be the result of functional disturbances which are only exaggerations of the normal fluctuations occurring in physiological mechanisms.

SLEEP. Cannon's concept of the parasympathetic as preserving and

restoring the bodily reserves suggests a somewhat broader generalization, namely, that *sleep* is essentially a parasympathetic integration. The evidence for this may be briefly summarized. In the first place, during normal physiological sleep various divisions of the parasympathetic outflow are active; thus, the pupils are constricted, peristalsis proceeds as does absorption in the gastrointestinal tract, the heart is slowed, and oxidation in the body as a whole is retarded. Furthermore, those processes are promoted which are essential for the building up and storage of chemical reserves. The extent to which the parasympathetic is actively engaged in the latter process, however, is not clearly established. The suggestive studies of Hess (1932) on the induction of sleep by faradic stimulation of the hypothalamic region of the brain-stem indicate the active participation of this region in the induction of sleep itself, and in the promotion of those vegetative processes which are known to occur during sleep.

SUMMARY

The autonomic system may be defined as that part of the nervous system innervating smooth and cardiac muscle and glands. There are two divisions; the *sympathetic* or thoracolumbar outflow, and the *parasympathetic* or craniosacral outflow. The sympathetic division is distinguished anatomically and physiologically from the parasympathetic by the position of the preganglionic synapses, those of the sympathetic being in the ganglion chain or prevertebral plexuses, while the synapses of the parasympathetic are found close to or within the tissues innervated. The sympathetic tends to discharge *en masse*, whereas the parasympathetic discharges discretely, *i.e.*, only one outflow, or part of one outflow is active at a time. A state of reciprocal innervation exists between the action of the sympathetic and parasympathetic, their effects tending to be antagonistic in respect of any given visceral organ.

The sympathetic system is thrown into activity during emotional crises, or in times of emergency. It is said to prepare the organisms for "fight" or "flight," and therefore it has command over those mechanisms essential for mobilizing the resources of the body for combat. Thus, it governs the vasoconstrictor innervation of viscera and skin, and when thrown into action tends to deplete those structures of their blood, causing a shift of circulating blood to organs essential for struggle, *i.e.*, to skeletal muscles, the heart and the brain. The blood vessels

of these organs are not constricted when the sympathetic system is active. Removal of the sympathetic chain from animals tends to cause lowering of body temperature, depression of the blood pressure, diminished capacity to withstand hemorrhage and fatigue, increased peristalsis of the gut and paralysis of the seminal vesicles, *i.e.*, ejaculation becomes impossible in the male although psychical orgasm is not abolished.

The parasympathetic system, discharging discretely, has widely differing effects upon different organs. Thus, in the head stimulation of the third nerve causes constriction of the pupils, but no other conspicuous parasympathetic action. Stimulation of the bulbar outflow causes increased salivation, peristalsis, flow of gastric secretion, liberation of insulin, and other actions which tend to restore the bodily reserves. Stimulation of the sacral outflow causes engorgement of the external genitalia with erection, and emptying of the hollow viscera; *i.e.*, bladder, seminal vesicles and rectum.

Speaking generally, the autonomic system serves to maintain the constancy of the internal environment of the body — homeostasis.

XIII

THE HYPOTHALAMUS: AUTONOMIC REGULATIONS

HISTORICAL NOTE

Knowledge of the hypothalamus is recent. Rokitsansky was aware as early as 1842 that basal meningitis is often associated with perforation of the stomach, and in 1890 Mauthner ascribed the somnolence of encephalitis to an infection of the base of the brain. This last conclusion received support in 1903 from the Italian neurologist Righetti, who found that somnolence occurred in 115 of 775 cases of cerebral tumour, and that in 61 per cent of those showing somnolence the tumour had affected either the pituitary or the third ventricle. About this time also Babinski (1900) and Fröhlich (1901) described cases of expanding tumours of the pituitary which gave rise to the syndrome of adiposity and sexual infantilism. Babinski and Fröhlich, however, did not attribute the syndrome to involvement of the brain, believing rather that it was a primary disturbance of the pituitary. This is scarcely surprising since, even today, pituitary and hypothalamic functions are so intimately bound up with one another that functional separation continues difficult.

The first experimental studies on the hypothalamic area are those of Karplus and Kreidl which appeared in a series of papers between 1909 and 1937. They found that stimulating the walls of the third ventricle in cats (later in monkeys) evoked changes in heart rate and blood pressure, as well as dilatation of the pupils, retraction of nictitating membrane and sweating. The reactions still occurred several weeks after removal of the cerebral cortex but were abolished by local application of cocaine. Karplus and Kreidl proved that these responses were mediated by the sympathetic system, since they disappeared when the peripheral outflow of the sympathetic was cut, or after high cervical section of the spinal cord. They found further that *reflex* dilatation of the pupil depended upon the integrity of the hypothalamus and not of the cerebral cortex. In 1912 Harvey Cushing encountered the adiposogenital syndrome after removing the pituitary gland, and after dividing the pituitary stalk. In the same year Aschner removed the pituitary of dogs by the transbuccal route without causing adiposity, and suggested that the adiposogenital syndrome which Cushing had precipitated in his temporal approach to the pituitary might be due to slight concomitant injury of the base of the brain. Weed, Cushing and Jacobson (1913) postulated autonomic control of the hypophysis and observed that piqué of the pituitary caused disturbances of carbohydrate metabolism.

The first deliberately to make lesions of the base were Camus and Roussy, who reported in 1913 that transitory polyuria developed if the hypothalamus of dogs was punctured through the sphenoid bone. In one dog a permanent polyuria developed along with adiposogenital dystrophy. The experiments were not described in detail until 1920, and Bailey and Bremer (1921a) published their now classical paper on experimental diabetes insipidus in which lesions restricted to the hypothalamic area invariably gave rise to polyuria, the polyuria being permanent if the lesion was large. They also observed transient glycosuria, adiposogenital dystrophy

and several instances of hypersomnia(1921b). After the publication of Bailey and Bremer's papers knowledge of hypothalamic functions developed rapidly. For review of clinical literature, see Fulton and Bailey(1929)and Miller(1942).

Recent history of the hypothalamus has turned largely upon the animal experimentation. Bard(1928)found that the hypothalamic area is concerned with the phenomenon of "sham rage." Keller(1930)established the hypothalamus as essential for heat regulation(see Keller, 1933, 1938). Cushing(1932)drew attention to the occurrence of acute gastrointestinal disturbance following surgical interference at the base of the brain, but we owe to the late Stephen W. Ranson and his collaborators, Magoun, Ingram, Fisher, Kabat, Clark, Hetherington, Harrison, Brobeck and others, a series of historically important papers on the relation of the hypothalamus to heat regulation, water metabolism, cardiovascular reflexes and sleep. Their work was summarized in a brief monograph by Ranson and Magoun (1939), and the whole field was discussed in greater detail at the meeting of the Association for Research in Nervous and Mental Disease held in December, 1939. The Association volume published in March, 1940 gives a well-considered précis on hypothalamic terminology, together with a full bibliography of some 1400 references(Peters, 1940). Since this volume is readily available, the present chapter will omit many citations prior to 1940 and concern itself principally with sources published since that time.

THE hypothalamus is a region of the brain in which highly organized visceral and somatic reaction-patterns are integrated. The fact that sweating, vasoconstriction, and changes in blood pressure can be obtained by stimulating the hypothalamus reveals little about its actual function. When, however, it is disclosed that through coördination of these individual mechanisms the hypothalamus maintains the temperature of the body relatively constant, regulates the level of blood pressure, adjusts water balance as well as sexual reflexes, the meaning of responses to stimulation is more evident, and it becomes necessary to consider these general integrations more in detail.

ANATOMICAL DIVISIONS

- | | |
|---|---|
| I. PERIVENTRICULAR REGION | N. supraopticus diffusus |
| Periventricular system | Anterior hypothalamic area |
| N. periventricularis preopticus | V. TUBERAL, INFUNDIBULAR MIDDLE REGION |
| N. periventricularis arcuatus | N. hypothalamicus ventromedialis |
| II. PREOPTIC REGION | N. hypothalamicus dorsomedialis |
| Medial preoptic area | Dorsal hypothalamic area |
| Lateral preoptic area | Posterior hypothalamic area |
| III. LATERAL REGION | Perifornical area |
| Lateral hypothalamic area | VI. CAUDAL OR MAMMILLARY REGION |
| Nn. tuberis laterales | Premammillary area |
| IV. ROSTRAL OR SUPRAOPTIC MIDDLE REGION | Supramammillary area |
| N. supraopticus | N. mamillaris medialis, partes medianus, medialis and lateralis |
| N. paraventricularis | N. mamillaris lateralis |
| N. suprachiasmaticus | N. intercalatus |

The hypothalamus, which is separated from the thalamus by a well defined sulcus, is closely associated, structurally and functionally, with the preoptic area. This general region of the base has been divided into six parts, each containing neurological elements of functional importance as given on opposite page (Rioch, Wislocki and O'Leary, 1940). From the physiological standpoint the nuclei of primary interest fall into four groups— anterior (n. supraopticus and n. paraventricularis), lateral (including lateral area), middle (including ventromedial and dorsomedial nuclei), and posterior (including posterior hypothalamic area and mammillary nuclei). Their anatomical characteristics may be summarized as follows:

Anterior group. The anterior group of hypothalamic nuclei include two principal cellular masses, the paraventricular nucleus (filiform), which forms a flat plate of cells lying close against the ependymal lining of the third ventricle, and the supraoptic nuclei. The *paraventricular* (fig. 57, Pv) are made up of large vacuolated cells with peripheral visceral granules and eccentric nuclei. Colloidal material found in the cytoplasm persists after hypophysectomy, and is believed by the Scharrers (1937, 1940) to be a secretory product.

The *supraoptic* nucleus (fig. 57, So; fig. 58A) lies immediately above the optic chiasm at the anterior end of the optic tract. It projects for a short distance along the anterior aspect of the tuber cinereum. This nucleus is of special interest physiologically because it gives rise to the supraopticohypophyseal tract which passes via the pituitary stalk to the neurohypophysis. Degenerative changes occur in the nucleus after destruction of the posterior lobe of the pituitary (Fisher, Rasmussen and many others). In the monkey such retrograde changes are more marked when the clip is placed high up on the pituitary stalk so that it compresses the median eminence of the hypothalamus.

Lateral group. The lateral group occupies the lateral part of the tuber cinereum and includes both the lateral area and the lateral tuber nuclei. The lateral area is more differentiated in man and anthropoids than in the lower mammals, and is of special interest physiologically because it is from this region that the majority of visceral reactions have been obtained on faradic stimulation (see below).

Middle group. The more medially situated nuclei are sometimes grouped with the ventromedial hypothalamic nucleus (fig. 57, Hvm) and the dorsomedial hypothalamic nucleus (Hdm), the nucleus tuberis (Tb). This region contains large cells which are quite distinct from the small-celled clusters of the nuclei tuberalis.

Posterior group. The posterior group includes the posterior hypothalamic area and the corpus mammillare which is made up of three discrete nuclear masses: the medial mammillary nucleus, the lateral mammillary nucleus, the nucleus intercalatus.

a. *Posterior hypothalamic area* (fig. 57, Hp; fig. 58). This area lies above and just rostral to the mammillary bodies, and, according to Le Gros Clark, consists of scattered large cells lying in a matrix of small cells all motor in function. The nucleus is important since it gives rise to one of the principal efferent projection

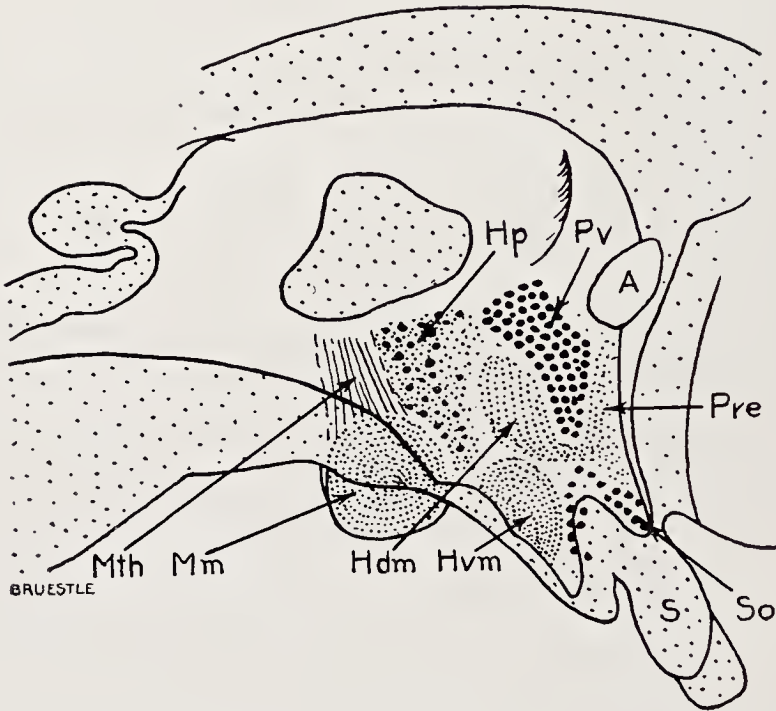


FIG. 57. Hypothalamic nuclei in man. A diagram after Le Gros Clark, showing principal nuclei projected on lateral wall of third ventricle from tracing of a photograph of human brain in which nuclei were subsequently reconstructed by serial section (*J. Anat.*, 1936, 70, p. 204).

A	Anterior commissure	On	Optic nerve
Hdm	N. hypothalamicus dorsomedialis	Pre	N. preopticus
Hp	posterior hypothalamic area	Pv	N. paraventricularis
Hvm	N. hypothalamicus ventromedialis	So	N. supraopticus
Mm	N. mamillaris medialis	S	Pituitary stalk
Mth	Mammillothalamic tract	Tb	N. tuberis

systems from the hypothalamus to the medulla and spinal cord. The fibres to the cord terminate in the lateral horns and thus establish a connection with the pre-ganglionic fibres of the sympathetic nervous system.

b. *N. corpore mamillare*. The mammillary bodies form conspicuous structures in the interpeduncular space on the base of the brain and are made up of several nuclear masses. The largest cell group, the medial mammillary nucleus (fig. 57, Mm), becomes highly developed in man and the higher primates. The lateral mammillary nucleus and nucleus intercalatus (Int.) are relatively small with small cells and as yet no specific function has been associated with them.

Periventricular region. In addition to these specific nuclear masses of the hypothalamus, there are, scattered practically throughout the whole region, very small cells almost without cytoplasm. As Bailey (1933) points out, their nervous nature is betrayed by their vesicular nuclei. They form the substantia grisea centralis which is a "substratum of relatively underdeveloped nervous cells out of which certain groups are differentiated into more or less definite nuclei."

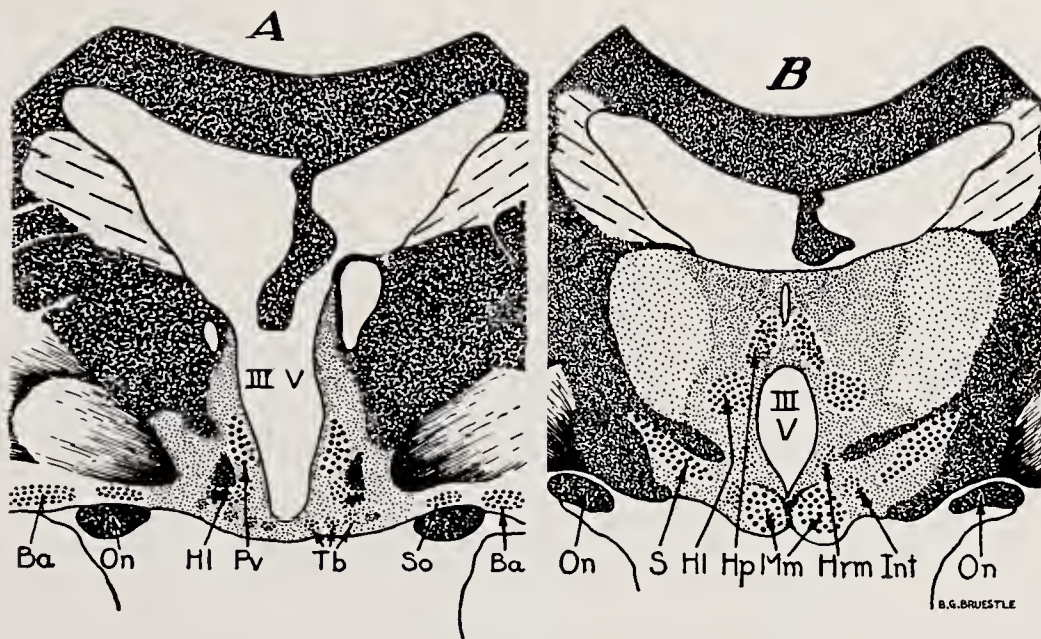


FIG. 58. Cross sections of human hypothalamus after Greving, lettered in accordance with modern terminology (for abbreviations see fig. 54). A, Section through anterior hypothalamus, showing paraventricular nuclei and tuber nuclei. B, Section through posterior hypothalamus, showing mammillary bodies and posterior hypothalamic nucleus (Hp) HI, n. hypothalamicus lateralis.

HYPOTHALAMIC CONNECTIONS. In Ingram's (1940) comprehensive survey of well-established hypothalamic connections he recognizes afferent, efferent and intra-hypothalamic fibre systems (fig. 59).

Afferent. The principal tracts passing into hypothalamus are: (i) medial fore-brain bundle, an ancient system connecting hypothalamus with the olfactory system, as well as with the septum; (ii) thalamohypothalamic fibres connecting the hypothalamus with the medial and midline thalamic nuclei. This system is important for relay of somatic and visceral sensory impulses to the hypothalamus. Connection with the anterior nuclei with the mammillary bodies, though long suspected, has not been clearly established; (iii) fornix fibres from the hippocampus to the posterior hypothalamus, particularly the mammillary; (iv) stria terminalis system from the amygdala establishes connection between the hypothalamus and this region of the vasoganglion; (v) pallido-hypothalamic fibres are well defined and establish a rich connection between the lenticular nucleus and the n. hypothalamus ventro-medialis; (vi) vago-supraoptic connections have been clearly demonstrated physiologically, but their anatomical course awaits confirmation.

Efferent connections are less numerous than the afferent and consist of the following: (i) Hypothalamothalamic systems include tracts from the mammillary nuclei to the anterior thalamic group (tract of Vicq d'Azyr) and periventricular fibres of uncertain destination; (ii) Mammillotegmental tract descending to tegmentum, but site of ending is unsettled; (iii) The periventricular system is probably the most important descending pathway from the hypothalamus since it arises in the posterior and lateral hypothalamic areas and passes to the spinal cord with

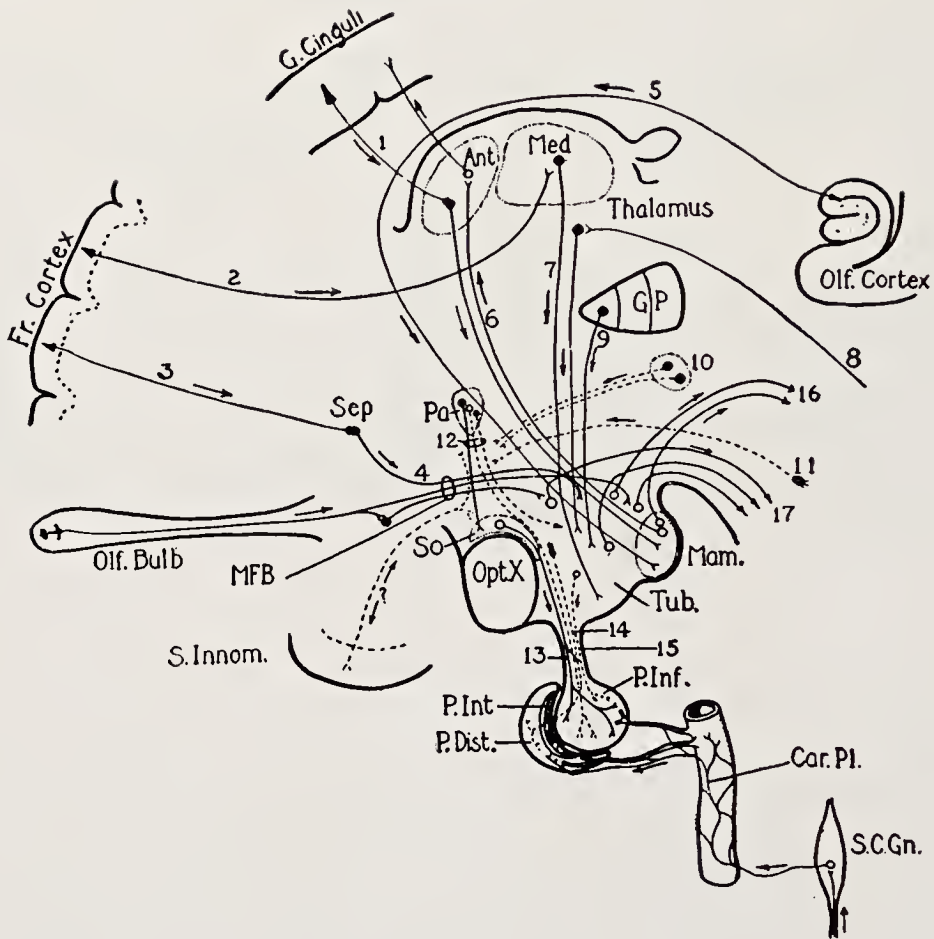


FIG. 59. W. R. Ingram's diagram of hypothalamic connections from E. Gellhorn's *Autonomic regulations*, 1943. Tracts indicated by broken lines have been postulated from physiological data and are not substantiated anatomically.

AFFERENT: 1, Corticothalamic. 2, Frontothalamic. 3, Frontoseptal. 4, Septohypothalamic. 5, Fornix. 6, Mammillothalamic. 7, Thalamohypothalamic. 8, Sensory systems ascending to thalamus. 9, Pallidohypothalamic. 10, Fibers from subthalamus and nucleus geniculatus lateralis pars ventralis(?). 11, Afferents from nucleus solitarius.

EFFERENT: 12, Paraventriculosupraoptic; paraventriculohypophysial; paraventriculo-tuberal. 13, Supraopticohypophysial. 14, Hypothalamico-anterior hypophysis connections. 15, Tuberohypophysial. 16, Fasciculus longitudinalis dorsalis. 17, Efferents descending through tegmentum. (Kind permission of Drs. Ingram and Gellhorn.)

Ant.	Anterior thalamic nuclei	Opt. X	Optic chiasm
Car. Pl.	Carotid plexus	Pa.	Paraventricular nucleus
Fr. Cortex	Cortex of frontal lobe	P. Dist.	Pars distalis of hypophysis
G. Cinguli	Gyrus cinguli	P. Inf.	Processus infundibularis
GP	Globus pallidus	P. Int.	Pars intermedia of hypophysis
Mam.	Mammillary nuclei	S. C. Gn.	Superior cervical ganglion
Med.	Dorsal medial thalamic nucleus	Sep.	Septum pellucidum
MFB	Medial forebrain bundle	S. Innom.	Substantia innominata
Olf. Bulb	Olfactory bulb	SO	Supraoptic nucleus
Olf. Cortex	Olfactory cortex	Tub.	Tuber cinereum

many secondary relay stations in the tegmentum and medulla. Associated with this system are other diffuse descending connections distributed widely in the brain system and medulla; (iv) Hypothalamohypophyseal connections to be described more in detail below, have a primary source in the supraoptic nuclei, and less well defined contributions from the paraventricular and tuber nuclei.

Intrahypothalamic connections have been demonstrated physiologically, but they have not been clearly established anatomically. The paraventricular-supraoptic connection has been established, and the paraventricular nucleus also sends fibres into the tuber region and probably also to the posterior hypothalamic area.

Supraopticohypophyseal tract. Within the past few years evidence has accumulated which clearly establishes the existence of a large tract, passing from hypothalamus to pituitary through the neural stalk. Rasmussen (1938, 1940) estimates in man that there are approximately 100,000 fibres in the stalk; in the monkey 50,000; in the rat 10,000. When the stalk is severed near to the pituitary (*i.e.*, just above the diaphragma sellae) the cells of the supraoptic nuclei undergo retrograde degeneration and disappear; in monkey's supraoptic nuclei cells diminished from 34,000 to 9,000. When the stalk was severed nearer the hypothalamus, the cells diminished in number from 34,000 to 6,000. Brooks and Gersh (1941) have traced certain of these fibres to specific cells in the posterior lobe complex, and they have described the character of their endings. Hair (1938) and Brooks (1938) have also traced a few fibres to cells in the anterior lobe. It is probable that the tuber nuclei as well as the supraoptic contribute to the nerve pathway to the pituitary. No one has determined whether this outflow is sympathetic or parasympathetic in its affinity, although Pickford (1939) has given evidence that the posterior lobe complex appears to be cholinergically activated. This would favor the assumption, well substantiated on other grounds, that the supraoptic is a parasympathetic nucleus. The secreting cells of the neurohypophysis, being nerve elements embryologically, become the equivalent of postganglionic neurons (parasympathetic), as with the secreting cells of the adrenal medulla (sympathetic). This no doubt gives fresh significance to the Scharrrers' (1941) disclosures concerning secretory cells in the anterior hypothalamic (1940) the preoptic nuclei of various animals. In the course of evolutionary development these specialized secretory units appear to have migrated in large part outside the diencephalon to form the neurohypophysis (Keller, 1942; see also Weaver and Bucy, 1940).

Innervation of anterior lobe (adenohypophysis). The *lobus glandularis* of the hypophysis includes *pars distalis* or anterior lobe, *pars tuberalis* and *pars intermedia* (Rioch, Wislocki and O'Leary, 1940). As already indicated, the anterior lobe receives some innervation via the neural stalk, but the recent studies of Zacharias (1942) indicate that it also receives important innervation from the Vidian ganglion from which small branches pass to the internal carotid plexus into the parenchyma of the adenohypophysis. Following bilateral ablation of the Vidian ganglion in rats the pseudopregnancy reaction develops, and insulin sensitivity was increased in 66 per cent of operated animals. The Vidian ganglion is formed by union of the parasympathetic root of the greater superficial petrosal nerve with the great deep petrosal nerve. This suggests that anterior lobe innervation, like that of the posterior lobe, is primarily parasympathetic in its affinities.

BLOOD SUPPLY OF HYPOTHALAMUS. Wislocki (1937) has indicated that the hypothalamic area is one of the most richly vascularized regions of the entire brain; in addition, the blood vessels of the infundibular area are more permeable to large molecules of certain dyes than are other vascular beds in the forebrain. The hypothalamic nuclei receive their chief supply from numerous small arterial branches

in the circle of Willis and its contributing arteries. The anterior communicating artery gives branches to the supraoptic region; the anterior cerebral artery supplies long tortuous branches which run on the under surface of the chiasm to the infundibular stalk. From the internal carotid are two branches which run on the under surface of the optic tract to the posterior part of the pituitary stalk. The posterior communicating artery likewise gives off several branches passing to the tuber region and generally supplies another large arterial branch to the mammillary bodies. It is thus possible to have softening of a single nucleus as a result of vascular occlusion of these smaller arteries(Le Blanc, 1926, 1928; Bailey, 1933).

The supraoptic and paraventricular nuclei have the richest vascular supply of any part of the central nervous system, save the *locus caeruleus*(Finley, 1940; Craigie, 1940), the capillary bed being six times more extensive per sq. mm. of tissue than the grey matter of the cerebral cortex. Many of the neurons in these nuclei are said to be pear-shaped structures, largely without dendrites, and each individual neuronal cell is literally surrounded by a maze of minute capillary channels. These morphological characteristics suggest, along with comparative anatomical evidence, that the neurons of the anterior group are specially adapted for responding to changes in the blood, be they chemical or thermal. Laidlaw and Kennard(1940) find barbiturate anesthesia causes dilatation of the capillary bed of the supraoptic and paraventricular nuclei, while ether anesthesia is associated with a relative constriction of these capillary channels. This suggests that primary activation of parasympathetic nuclei is essential to the mechanism of barbiturate anesthesia, as contrasted with ether, which acts on the nervous system as a whole. For details concerning the vascular supply of the hypothalamus of man see Foley, Kinney and Alexander(1942).

VISCERAL FUNCTIONS

That reflexes involving the autonomic nervous system are integrated at some focus between the inferior colliculi and the basal ganglia was obvious for many years, for Goltz's decorticated dogs had well developed autonomic reflexes, while Sherrington's decerebrated dogs and cats failed to show such reactions. It was not until 1928, however, that Philip Bard established the posterior hypothalamus as largely responsible for the differences in autonomic function between decerebrate and decorticate animals. When both cerebral hemispheres are removed, especially if the ablation is acute, periodic discharges occur affecting all divisions of the sympathetic system. These discharges are accompanied by signs of anger which Cannon(1929) and Bard(1928) designated "sham rage." During the outbursts, the pupils dilate, the hair stands on end, the heart rate increases, blood pressure rises, salivation occurs and there are other signs of sympathetic hyperactivity. With section of the brain stem at more rostral levels Bard found that the reactions continued until the posterior hypothalamic area was excluded; the reactions then ceased. Another body of evidence entirely in harmony with that of Bard was

brought forward by Beattie, Brow and Long(1930), who observed that the heart rate of thalamic animals was subject to extraordinary fluctuations. Electrocardiographic examination revealed that extrasystoles were prone to occur during the periods of irregular pulse. Similar bouts of extrasystolic arrhythmia also occur during chloroform narcosis; when the stellate ganglia were both removed, the systolic arrhythmia ceased. They could abolish it similarly by cutting the ventral nerve roots corresponding with the preganglionic sympathetic supply to the heart; the effect could also be destroyed by sectioning the medial longitudinal bundle in the medulla. They traced it back to the posterior hypothalamic area and, like Bard, found that the arrhythmia disappeared if the posterior hypothalamic nuclei were excluded. Here then was positive evidence of sympathetic hyperactivity initiated in posterior diencephalon.

HYPOTHALAMIC STIMULATION. A relatively huge literature has grown up recording effects of electrical and chemical stimulation of the hypothalamus area in acute unanesthetized preparations, as well as in chronic decorticate animals; the Horsley-Clarke technique of stimulation has also been extensively utilized in intact lightly anesthetized animals.* As far as the posterior hypothalamus is concerned, recent results coincide with those originally reported by Karplus and Kreidl(discharge of the sympathetic system), and there has been a mounting body of evidence indicating that *parasympathetic* mechanisms may be specifically activated by electrical excitation of the tuber and anterior hypothalamic nuclei. Beattie and Kerr (1936) and Magoun(1938) have evoked bladder contraction, and increased gastric pressure and peristalsis have been recorded by Beattie and Sheehan(1934) and by many others. Beattie has also disclosed cardiac slowing and vasodilatation from stimulation of the tuber nuclei, as have Wang and Ranson(1939). Save for the relatively clear-cut functional separation of the areas of sympathetic and parasympathetic representation, respectively, stimulation studies have given little information concerning the wider functions of the hypothalamic area as a whole. More detailed summaries of stimulation effects were given in the first edition of this book, also in the reviews of Ranson and Magoun(1939) and in the reports of the meeting of the Association for Research in Nervous and Mental Disease for 1940, and in the important papers of Hess(1932a&b).

The excitability of the posterior and lateral hypothalamic areas has been subjected to careful analysis in a series of papers by Pitts and his collaborators(Bronk, Pitts and Larrabee, 1940; Pitts, Larrabee and Bronk, 1941; Pitts and Bronk, 1942). With a single postganglionic fibre of the cervical sympathetic isolated they find that this neuron responds less rapidly than the rate at which the hypothalamus is stimulated. Thus, at ten per sec. the postganglionic neuron discharged once every few seconds, but at 100 per sec. stimulus rate the sympathetic neuron discharged regularly at six per sec. The two sides of the hypothalamus summate with one

* The barbiturates, when used as anesthetics, selectively abolish the excitability of the hypothalamic nuclei(Masserman, 1937) leaving the excitability of the cerebral cortex essentially normal(Fulton, Liddell and Rioch, 1930).

another in driving an isolated postganglionic neuron, indicating that multiple pathways descend from both sides of the hypothalamus to make connection with each sympathetic neuron. No qualitative differences were noted as between the lateral and posterior nuclei. Evidence was obtained that the majority of the descending pathways has synaptic connections in the medulla, and that afferent stimulation acting upon these medullary relay stations ("buffer" neurons) may inhibit the effects of hypothalamic stimulation. Pitts and Bronk (1942) have studied the excitability cycle of the hypothalamic nuclei; following activity they find evidence of a period of subnormal excitability similar to that observed in neurons of the cerebral cortex and spinal cord.

J. C. White (1940) has reported upon the effects of stimulating the hypothalamus in conscious human beings and was able to induce marked cardiac acceleration from the posterior area (5 cases), while cardiac slowing occurred when the medial preoptic area was faradized, and from this area also a sleep reaction appeared to be induced. Atropine abolished the bradycardia from such stimulation. It is interesting that sleep was induced from the area which exhibits vasodilatation during barbiturate anesthesia.

WATER METABOLISM (*Diabetes insipidus*). The work of Fisher, Ranson and their collaborators, together with the more recent studies of Gersh, has given a definitive solution to the previously perplexing problem of diabetes insipidus. It had long been known that lesions of the hypothalamic area, *e.g.*, third ventricle tumours, were often associated with abnormal amounts of water excretion. In some human cases of diabetes insipidus the 24-hour urine output has amounted to as much as 20 litres. It had been recognized that pituitrin (the pitressin fraction) curtailed abnormal thirst and polyuria in such cases, but curiously enough, removal of the posterior lobe of the pituitary (neurohypophysis) does not induce polyuria in man or experimental animals (Ingram and Fisher, 1936; Keller, 1942). Similarly, it was not ordinarily induced by section of the pituitary stalk, although Mahoney and Sheehan (1936) found that if the stalk were severed close to the infundibulum, diabetes insipidus might in these circumstances follow. In keeping with this Ingram and Fisher find that *when the posterior lobe plus the stalk is removed lasting polyuria* results. With Richter (1938), they believe that sufficient posterior lobe tissue exists in the stalk to account for the failure to produce diabetes insipidus by section of the stalk alone. Richter and others have pointed out that diabetes insipidus also depends upon the integrity of the *anterior lobe*; in harmony with this, Keller, Noble and Hamilton (1936) record the following important experiment: After polyuria was well established in a dog (hypothalamic lesion), hypophysectomy caused the polyuria to disappear abruptly. If then anterior lobe extract was admin-

istered subcutaneously, polyuria was again precipitated, rising to a maximum after 12 days. Keller(1937, 1942)believes this due to thyrotropic activation of the thyroid, since polyuria can also be precipitated in such an animal by thyroid feeding. Mahoney and Sheehan(1935)found, in accordance with this, that thyroidectomy also abolished a well established polyuria in dogs.

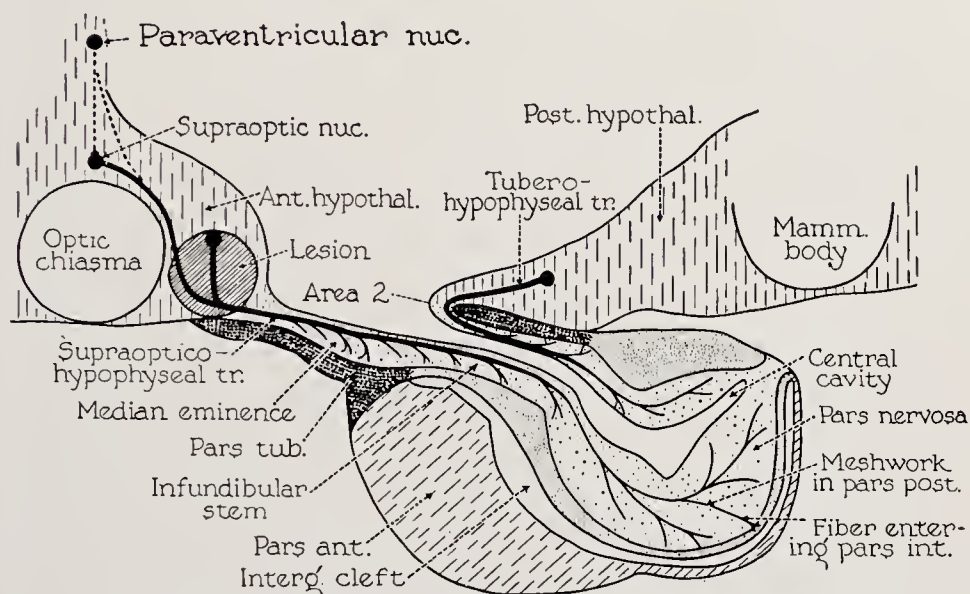


FIG. 60. Longitudinal section of cat's hypothalamus, showing tractus supraoptico-hypophyseus, whose interruption causes diabetes insipidus.(From the monograph on diabetes insipidus by Fisher and his collaborators, 1938.)

In a series of well conceived experiments Fisher, Ingram and Ranson (1938)found that bilateral destruction of the supraoptic nuclei is followed by pronounced diabetes insipidus in experimental animals(fig. 60). Following such lesions nearly all fibres of the supraopticohypophyseal tract were found to degenerate, and with this degeneration the secreting cells of the neurohypophysis likewise disappeared. The posterior lobe cells are thus so intimately dependent upon their innervation that once this is destroyed, the cells themselves undergo atrophy and die—and diabetes insipidus develops.

It remained for Gersh(1939)to give a rational explanation of why diabetes insipidus does not follow posterior lobe ablation. In rats, following buccal hypophysectomy Gersh observed that parenchymal cells sur-

rounding neural stalk and base of infundibulum(homologous with those of the posterior lobe complex)promptly underwent hypertrophy as judged by increase in number of secretory granules, and that these remaining cells no doubt were able to elaborate a sufficient quantity of antidiuretic hormone to prevent the development of polyuria. To quote Gersh:

“The specific parenchymatous cells of the neurohypophysis of the rat are clearly distinguished from neuroglia cells elsewhere in the central nervous system by their characteristic cytoplasmic inclusions. The glandular cell is present in all orders of Mammalia examined whose glands have yielded the antidiuretic substance. The distribution of the glandular elements is strictly limited to the sites from which the antidiuretic substance has been extracted. The specific, differentiated quality of these cells is already present at the time when the active substance has been extracted from the gland for the first time. Finally, in the adult, cytological changes in these cells coincide with physiological fluctuations in the rate of secretion of the antidiuretic substance into the blood stream. These coincidences are too striking to be regarded merely as accidental; they are proof of the conclusion that the parenchymatous glandular elements of the neurohypophysis produce and secrete the antidiuretic substance. The observations coincide with the requirements of the most widely accepted theory of diabetes insipidus.”

Keller(1942)in a searching, critical examination of the Ranson-Gersh theory of diabetes insipidus reaches essentially the same conclusion, but he indicates that some of the cells producing the antidiuretic hormone may reside in the hypothalamic nuclei themselves as suggested by the work of the Scharrers(1940; see Weaver and Bucy, 1940). Gersh and Brooks(1941)have demonstrated that these secretory cells of the posterior lobe complex receive innervation from the supraopticohypophysial system. Hence, only when the neurons of origin are destroyed can all of the secreting cells of the neurohypophysis be put out of action. From these studies it has become clear that the kidney tubules are as intimately under the control of the nervous system as if they received a direct innervation, and it is no accident that the part of the brain exercising this control over the kidneys is also the region responsible for controlling water loss through other channels.

HEAT REGULATION. Following up their brilliant analysis of water metabolism in diabetes insipidus Ranson and his collaborators turned their attention to the problem of heat regulation. Writing in June, 1932, Keller and Hare had stated, “the chief central mechanism controlling heat production is located in the hypothalamus, and that extirpation of this region releases the heat loss mechanism, located elsewhere, from co-

ordinated control." * Taking the subject up from this point, Magoun, Harrison, Brobeck and Ranson(1938)disclosed by local heating(high frequency currents passing between two implanted electrodes)in cats that the mechanisms of heat loss, especially panting, are activated when the temperature of the anterior hypothalamic area is raised. The region included a cube about 8 sq. mm. in extent lying in the midline immediately above the optic chiasm and extending rostrally into the preoptic area and no other part of the forebrain. The responses could not be obtained when the electrodes were applied more than 4 mm. from the midline. The generalized panting began within about thirty to sixty seconds after the application of the heating current and was accompanied by sweating of the pads of the feet and by some vasodilatation. Rectal temperatures always fell several degrees centigrade as a result of the panting and sweating, but the extent of the fall is not reported(see also Hemingway, *et al.*, 1940).

Since the mechanisms of heat production are activated by the posterior hypothalamus, it follows that they are primarily governed by adrenergically(sympathetic)innervated structures coupled with the somatically controlled shivering reflex; the mechanisms of heat loss, on the other hand, are primarily governed by cholinergic(parasympathetic)mechanisms including sweating, vasodilatation, etc., coupled with the somatic reaction of panting. The function of maintaining body temperature is thus a highly integrated reaction involving both divisions of the autonomic system, as well as important somatic reactions.

Mechanisms of heat loss. The primary mechanisms of heat loss are: peripheral vasodilatation, panting and sweating. In addition to this, suppression of metabolic activities may diminish heat production. *Panting* can be induced by hypothalamic stimulation, and in the decorticate preparation the threshold for evoking panting is somewhat lower than in the normal animal; it does not occur in the oblongata animal(Keller, 1933). Lilienthal and Otenasek(1937)find that polypneic panting continues in decorticate cats so long as the "caudodorsal" part of the diencephalon is intact including unspecified nuclei of the metathalamus and superior hypothalamus; the ventral hypothalamic nuclei are not essential. *Vasodilatation* is readily obtained from anterior hypothalamic stimulation, and falls in blood pressure have

* Dr. Keller's studies on this subject began in 1929 at Yale University and a preliminary communication on heat regulation in brain stem preparations was made April, 1930 and again in 1933, but detailed description of this historically important investigation did not appear until November, 1938. Although Isenschmid and Schnitzler(1914)had suggested much earlier that the hypothalamus is concerned in heat regulation, their work was overlooked and Keller must be given credit for having first clearly proved that the hypothalamus is essential for temperature regulation.

been reported from the anterior region; such depression can also be obtained from the cerebral cortex (ch. xxiii). When the hypothalamus is removed, profuse vasodilatation occurs, again suggesting a release of the heat-loss mechanism. *Sweating*, one of the most effective means of lowering the temperature, was observed by Karplus and Kreidl (1910) in response to hypothalamic stimulation, and was studied in detail by Hasama (1929). The primary focus appears to be in the region of the tuber nuclei.

Mechanisms of heat production and conservation. The most important mechanisms of heat production and conservation are shivering, mobilization of carbohydrate reserve, vasoconstriction, piloerection, increase in heart rate, and elevation of metabolic activity. These reactions, with the exception of shivering, can all be obtained from faradic stimulation of the lateral hypothalamic areas. When a hypothalamic preparation is placed in a cold atmosphere, shivering occurs, vasoconstriction can be demonstrated in exposed surfaces; there is piloerection which tends to prevent the irradiation from the body. All these reactions, except shivering, may be induced by discharge of the sympathico-adrenalin mechanism. The phenomenon of shivering is of special interest and will be given separate consideration.

All available evidence thus points to the anterior hypothalamus as the region primarily concerned with the mechanisms of heat loss. The cat with an anterior hypothalamic lesion is unable to regulate against heat, but its capacity to regulate against cold is unimpaired (Keller, 1936; Teague and Ranson, 1936). With larger lesions, such as those of Frazier, Alpers and Lewy (1936) and Keller's earlier lesions, the animal loses control over both the mechanisms of heat loss and heat production. In the case of *monkeys*, evidence of localization of the heat loss mechanism is even more impressive. Thus bilateral lesions affecting the paraventricular, supra-optic and lateral hypothalamic nuclei cause transient hyperthermia as in cats, the body temperature rising to a dangerously high level when the animal is placed in a hot room (Ranson, Fisher and Ingram, 1937). It is possible that the medial nuclei are also involved, for in cats and in Alpers' (1936) clinical case of hyperthermia, marked disturbance of heat loss mechanisms followed a medial hypothalamic lesion involving the tuber nuclei. In monkeys, as well as in cats and man, medial destruction of the posterior hypothalamus causes hypothermia and enduring incapacity to regulate against cold. At present all available evidence points to the medial nuclei as being the more significant for regulation both against heat and cold.

The mode of action of the antipyretic drugs has a direct bearing upon these physiological considerations, for all such agents act upon the hypothalamic mechanisms, generally impairing both the anterior and posterior nuclear masses (Masserman, 1937). A human being under anesthesia induced by the barbitol derivatives — *e.g.*, dial or sodium amytal — is reduced to the poikilothermic level, having little or no capacity for heat regulation. As the anesthesia becomes less deep, the first mechanism to emerge is generally shivering, and then the other heat producing agencies (see below, on hyperthermia).

Shivering. The body's most potent means of elevating its temperature lies in the reflex act of shivering. In the intact animal, this complex mechanism, though supraspinal in basic organization, involves all levels of nervous integration. Sherrington (1924) finds that a spinal dog, well recovered from spinal shock, does not shiver below the level of its spinal

transection when exposed to cold, and that because of this its hind quarters become cooler than the head (vaginal temperature lower than mouth). Bodily combustion may be increased by as much as 400 per cent in a vigorous shivering response (Beattie, 1938). Bazett, Alpers and Erb (1933) and others have found that the shivering reflex depended upon the integrity of subcortical forebrain nuclei, and Beattie and Kerr (1936) report that the essential region lies in the caudal half of the medial portion of the thalamus. Elevation in temperature of the blood passing through the diencephalic area is an adequate stimulus for shivering, but impulses from cold receptors in the skin may also precipitate shivering (Jung, *et al.*, 1937). Exaggerated shivering responses occur in animals with cortical lesions, especially bilateral lesions of area 4 (Aring, 1935). This indicates, as does the work of Pinkston, Bard and Rioch (1934), that the cerebral cortex also plays a significant part in thermal regulation.

Though an animal with lesions of the hypothalamus cannot shiver, Keller and Hare (1932) have recorded the now well substantiated fact that oblongata animals, when suddenly exposed to a very low temperature, do actually exhibit shivering movements; but the reaction is insufficient to maintain the temperature of the body normal, and the movements are poorly coördinated as compared with the vigorous shivering reflexes of the decorticate animal.

OBESITY.* Hypothalamic obesity was first reported by Mohr (1840) in a patient with a hypophysial tumour, but it is now generally known as one characteristic of the syndrome described by Fröhlich (1901). Erdheim (1904) deserves credit for first attributing this particular symptom to hypothalamic rather than to hypophysial damage. The changes which follow experimental lesions of the hypothalamus have justified Erdheim's hypothesis (Aschner, 1912; Smith, 1927; Hetherington and Ranson, 1940), and the pituitary gland is no longer considered to be necessarily involved in obesity of this kind. In clinical practice, however, hypophysial tumours remain one of the most frequent causes of the hypothalamic involvement which causes adiposity.

The neurons which must be destroyed to bring on adiposity have not yet been identified. Hetherington and Ranson (1942) have made a careful study of relatively discrete lesions which caused obesity in albino rats; they found bilateral involvement of either the ventromedial nuclei or the region dorsolateral to the mammillary bodies. In the monkey this

* I am indebted to Dr. John Brobeck for drafting the section concerning obesity and blood sugar levels.

type of obesity develops following superficial lesions of the base of the anterior hypothalamus (Brooks, Lambert and Bard, 1942), and also after damage to the ventrocaudal portion of the thalamus and rostral mesencephalic tegmentum (Ruch, Blum and Brobeck, 1941; fig. 61).

There remains little doubt that the greater part of the material deposited as fat represents surplus food ingested by the affected animals (Keller, Hare and D'Amour, 1933; Brobeck, Tepperman and Long, in



FIG. 61. Obesity in a rhesus monkey following a bilateral Horsley-Clarke lesion in the rostral mesencephalic tegmentum just posterior to the hypothalamus. From unpublished studies of Ruch, Shenkin and Patton. On February 24, 1942, the day of operation, the animal weighed 3.1 kg.(left). On April 16, 1943, the animal weighed 12.9 (middle and right). When arms are extended the animal is unable to hold his head erect (middle).

preparation), and the name *hypothalamic hyperphagia* has been given to the primary disturbance caused by appropriate lesions. Although the cause of the increased food intake is as yet unknown, the discovery of the hyperphagia has provided at least a hypothetical basis for study of the overeating of obese human individuals. Wilder (1932) has already suggested that ordinary clinical adiposity may be the result of "functional" involvement of the same centres, destruction of which produces typical experimental hypothalamic obesity.

REGULATION OF BLOOD SUGAR LEVELS. Abnormalities of carbohydrate metabolism have frequently been attributed to hypothalamic lesions. Experimental evidence to justify this conclusion, however, is unsatisfactory except for the hyperglycemia which can be produced by stimulation of the lateral hypothalamic area (Himwich and Keller, 1930; Magoun,

Barris and Ranson, 1932), or by hypothalamic injury as an acute phenomenon (Aschner, 1912; Camus and Roussy, 1920; Barris and Ingram, 1936; and many others). This increase of the blood sugar is probably brought about by activating at the hypothalamic level the sympatho-adrenal medullary system which can also be stimulated at the level of the splanchnic nerves, in the spinal cord, or at the medulla oblongata (Houssay and Molinelli, 1925).

On the other hand, anterior hypothalamic lesions have been reported to cause hypoglycemia (D'Amour and Keller, 1933; Barris and Ingram, 1936) as well as increased sensitivity to the hypoglycemic effect of insulin (Cleveland and Davis, 1936; Ingram and Barris, 1936). In contrast to the hyperglycemic effects noted above, the mechanism of production of this hypoglycemic tendency remains completely obscure, and the propriety of regarding it as a specific hypothalamic effect has been seriously questioned (Long, 1940). The report that hypothalamic lesions may minimize the effects of pancreatectomy in the cat (Davis, Cleveland and Ingram, 1935) has lacked confirmation and has recently been contradicted by Brobeck and Long (in preparation). These latter authors were unable by hypothalamic lesions to ameliorate the diabetes of partially pancreatectomized rats; moreover they were able actually to precipitate diabetes in susceptible animals by placing lesions which increased the food intake of the rats — that is, by hypothalamic hyperphagia.

Clinical application of these experimental data is at the present time rather hazardous with the possible exception of the sympathetically induced hyperglycemia first mentioned. The entire subject awaits more adequate and more intensive study.

BASAL METABOLISM. Haney (1932), using CO_2 production as an index, reported that stimulating the distal cut end of the cervical sympathetic of rabbits caused an augmentation of basal metabolic rate of 22 to 29 per cent. Using O_2 consumption Friedgood and Bevin (1939) observed more moderate increases from such stimulation as did Brock, *et al.* (1940), but the latter authors found that severing the cervical sympathetic in cats and rabbits causes a persistent fall in B.M.R. of 15 to 35 per cent. Friedgood and Cannon (1940) confirmed this result but concluded that these effects are not due to direct innervation of the thyroid, since the metabolic depression still occurs if the sympathetic chain is severed above the superior cervical ganglion. Uotila (1940), moreover, has given convincing evidence that the thyrotropic hormone of the an-

terior lobe is activated by the hypothalamus during exposure to cold, and that the activation is effected both via the stalk and the cervical sympathetic. This places the thyroid squarely under hypothalamic control.

MISCELLANEOUS FUNCTIONS ATTRIBUTED TO HYPOTHALAMUS. Many other visceral functions have been attributed to the hypothalamus. The more important of these are regulation of certain phases of sexual and gastrointestinal activity, blood pressure and sleep.

Sexual functions. Isolated injuries of the midline tuber nuclei have caused sexual disturbances in all mammals so far studied, but it is now clear that the sexual aberrations following hypothalamic injury can be separated from adiposity which results from such injury (usually elsewhere in the diencephalon; see above). In analyzing the relation of the hypothalamus to sexual function Bard (1940) has studied the neurological levels of sexual behaviour. Animals having estrus cycles show at the height of estrus highly organized patterns of sexual behaviour prior to, during and after mating. Bard finds that decorticate cats may exhibit typical estrual behaviour, but he was unable to determine at what level these patterns were integrated. After exclusion of the basal ganglia and the anterior hypothalamus, estrual behavior continues following injection of estrin, and in certain animals it was little modified when the posterior hypothalamus was encroached upon. Evidently, therefore, estrual behaviour is organized at some level rostral to the lower portion of the mesencephalon.

Brooks (1938, 1940; see also Brooks, Bojar and Baederkoff, 1940) has studied the relation of the hypothalamus to ovulation, finding in the rabbit, as in the ferret, that section of the pituitary stalk, destruction of the tuber nuclei or ablation of the anterior lobe of the pituitary abolishes postmating ovulation; stalk section likewise abolishes the ovulation normally induced by picROTOXIN and metrazol (Gellhorn, 1943). In the rat Dempsey and Searles (1943) have demonstrated that section of the stalk affected estrus cycles in only half their animals, and that it did not invariably abolish postmating ovulation. The guinea pig similarly may show normal estrus cycles after stalk section, but Dempsey and Uotila (1940) have demonstrated by exposing the animals to cold (causing marked lengthening of cycles) that the hypothalamus regulates the rate of secretion of gonadotropic hormones. In animals with stalks cut, exposure to cold had no effect on cycles. As with many other endocrines, therefore,

the gonadotropic hormone of the anterior lobe is normally regulated by the nervous system, and delicacy of adjustment is no doubt achieved through such integration, but in the absence of nervous control secretion continues without coördinated adjustment. This likewise appears true of the islets of Langerhans, adrenal cortex, thyroid and parathyroid secretions.

Gastrointestinal activity. The relation of the hypothalamus to the gut had been little studied until 1932 when Cushing published his Balfour lecture on peptic ulcer and the interbrain, in which he attributed the severe gastrointestinal disturbances which often follow surgical procedures involving the base of the brain to hypothalamic injury. Inhibition of gut motility by hypothalamic stimulation was mentioned by Karplus and Kreidl (1910). Beattie and Sheehan (1934), under the stimulus of Cushing's work, found in fasting cats under chloralose anesthesia that stimulation of the tuber region caused increased intragastric pressure and augmented peristaltic movements of the stomach, the effect being abolished by vagal section; whereas excitation of the posterior hypothalamus caused a fall in intragastric pressure and complete obliteration of all gastric motility. This has been confirmed by Masserman and Haertig (1938) and many others (Sheehan, 1940).

Those who first reported upon the effects of hypothalamic lesions did not study the gut. Recently, however, more attention has been focussed upon the gastrointestinal tract; thus, following diencephalic lesions in a series of 17 monkeys, profound gastrointestinal disturbances were encountered, accompanied by gastric and duodenal erosions, bleeding and, in two instances, perforation of the stomach (such lesions also cause cardiac irregularities) (Watts and Fulton, 1934). In another series of 16 monkeys with more restricted hypothalamic injury, five showed multiple hemorrhagic foci in the gastric mucosa, and in all five the lesion was restricted to the tuber nuclei (Hoff and Sheehan, 1935). In a series of several hundred control observations, with the lesions elsewhere in the nervous system of monkeys, few corresponding gastric disturbances were encountered, except occasionally following simultaneous bilateral removal of the motor and premotor areas of the cerebral cortex (Kennard and Willner, 1941b). Keller and D'Amour find corresponding gastric disturbances in dogs following tuber lesions. If the dogs are previously sympathectomized, the hemorrhagic lesions of the mucosa fail to occur, but ulcers with crater formation were encountered. Keller (1936b&c) is, therefore, of the opinion that hemorrhage from the mucosa depends on the integrity of the sympathetic system and that ulcer formation occurs only when the parasympathetic nerves (vagi) are intact. Further studies following this important lead by Keller are needed. Death from acute gastric hemorrhage has occurred in a young and healthy chimpanzee following hypophysectomy (and presumed injury to the hypothalamus; Mahoney, unpublished; see also Masten and Bunts, 1934).

Blood pressure regulation. The position of the neurohypophysial mechanism in

relation to blood pressure regulation has not been adequately worked out. However, it is clear that the posterior hypothalamus is capable of precipitating abrupt and often dangerous elevations of the systolic pressure. The oblongata animal maintains its blood pressure at a steady level, whereas the posterior hypothalamic animal of Bard during bouts of sham rage has conspicuous elevation of systolic pressure with each sympathetic outburst. Similar fluctuations are known to occur in normal animals and in human beings during anger; these fluctuations are no doubt mediated from the cortex via hypothalamic centres. Some have suspected that hypertensive states of neurogenic origin arise from the cerebral cortex and hypothalamus, partly through direct activation of the vasoconstrictors, and partly by liberation of pressor substances of endocrine origin. Splanchnic section has, in certain instances, reduced to normal levels the systolic pressure in long-standing cases of human hypertension, but generally after the splanchnics are cut the pressures tend again to rise. The pituitary itself has also been suspected of playing a part through its potent vasoconstrictor "pitressin." Recently, Page and Sweet(1937) have induced hypertension in dogs by constricting the renal arteries, and they report that subsequent hypophysectomy reduced pressures of 240/160 mm. Hg to pressures varying from 150/100 to 90/40 Hg. In general, however, the pressure tended after several months to rise again. Rasmussen and Gardner(1940) record a dramatic fall in systolic pressure in a victim of malignant hypertension as a result of section of the pituitary stalk.

Since adrenalin acts primarily on the arterioles and pituitrin on the capillaries, it is logical to think that these two substances, acting synergically on the peripheral resistance, would, if liberated in excess quantities, maintain the blood pressure at an abnormal level. Since both substances may be liberated at the behest of the nervous system, it is clear that states of hypertension may be induced and maintained by central action. The important experiments of Prinzmetal and Clifford Wilson(1936) do not exclude the existence of hypertensive states of neuroendocrine origin(see Page, 1942).

SOMATIC FUNCTIONS

All levels of central nervous integration so far studied have exhibited a dovetailing of autonomic and somatic representation, and the hypothalamus is no exception. It is true, however, that in the ascending scale of animals somatic integrations assume a less important role at the hypothalamic level than in lower forms such as cat and dog. A hypothalamic cat is capable of executing essentially normal locomotor movements, and Hinsey(1940), who has studied the somatic functions of the hypothalamus, finds that well defined postural and phasic movements can be induced by stimulation of the posterolateral hypothalamic and subthalamic areas. He believes that these movements are brought about through motor projections from the diencephalon to the subthalamus — thence to the brain stem and spinal cord. Waller(1940) has given more precise localization, stating that the locomotor point for running movements is actually in Forel's field at the level of the subthalamic decussa-

tion, dorsal to the mammillary body and near the subthalamic body of Luys. Similar localization was given by Ectors, Brookens and Gerard (1938).

There is little data concerning primate hypothalamus and somatic integration. Respiratory movements, *e.g.*, panting, are undoubtedly influenced from this level, but the hypothalamic monkey is unable to execute locomotor movements, and primary somatic movements have so far not been reported as resulting from hypothalamic stimulation. In the primates it would appear that somatic integrations have been largely taken over by the basal ganglia and cerebral cortex.

CLINICAL IMPLICATIONS

Clinical literature relating to the hypothalamus and the disorders arising from its injury has increased rapidly within the last few years, and has recently been summarized by Vonderahe(1940)and Bailey(1940). It is possible to recognize five distinct syndromes of the hypothalamus, four representing destruction and one periodic irritation of diencephalic centres. The first four syndromes may dovetail with one another, and rapidly expanding tumours of the hypothalamic area may cause all four to merge into one. The syndromes in question may be designated as follows:(i)hyperthermia,(ii)diabetes insipidus and emaciation,(iii)the adiposogenital syndrome,(iv)hypersomnia with disturbed thermal regulation, and(v)autonomic epilepsy.

PSYCHIATRIC CHANGES. With all five of these syndromes there are likely to be changes in personality, varying from simple depressions to outspoken manic states, contamination neuroses and other psychiatric alterations, which may even simulate the major psychoses.* Corresponding changes in behaviour among animals subjected to hypothalamic lesions have frequently been noted(Bard, 1934). From the point of view of localization, lesions of the anterior hypothalamus tend to produce excited states(Fulton and Ingraham, 1929), while posterior lesions are likely to be accompanied by lethargy, indifference, depression, with a tendency towards catatonia(Harrison, 1940). It is beyond the scope of a physiological text to discuss these behavioural aberrations in detail, but

* The literature on the relation of the hypothalamus to psychiatric states has become extensive. Fulton and Bailey(1929)examined the effects of third ventricle tumours on mental status, Alpers(1940)and Masserman(1941)the relation of the hypothalamus to emotion and personality and Morgan(1940)the cell changes in the hypothalamus in the major psychoses. Each of these papers has a full bibliography.

they should always be sought in cases of hypothalamic disturbance, particularly in encephalitis lethargica, which has done so much, especially in children, to increase the incidence of psychopathic conditions throughout all civilized countries. This obvious correlation between organic lesions of the nervous system and mental aberrations deserves more careful study than it has received in the past, and it suggests that more attention should be devoted to the necropsy study of the hypothalamus in the major psychoses (Morgan, 1940).

HYPERTHERMIA. Experimental lesions of the anterior hypothalamus in animals and surgical intervention involving this area in man are often followed by alarming and persistent elevations of body temperature. Lesions of the posterior nuclei, on the other hand, are prone to induce states of *hypothermia*. Zimmerman (1940), Davison (1940) and others have reported cases of hyperthermia associated with isolated hypothalamic tumours in man. One of the most striking is that of Zimmerman:

CASE 4. V.S. White male, 71 years of age, with hyperthermia of 1 year's duration. Meningeal lipoma destroying the ventromedial tuberal nuclei, part of the right mammillary body and the right mammillothalamic tract.

History. This patient was a 71 year old Italian priest who first entered the New Haven Hospital in August 1931, complaining of gastric disturbances which were characterized by gaseous eructations, sourness and constipation. Despite an alleged loss of 30 lb. in weight, he was distinctly obese, with pitting edema over the ankles. He was very hypochondriacal and apprehensive and exhibited early senile mental changes. The temperature was 100° F., rising to 100.5° F. on but three occasions. Roentgenograms of the alimentary tract and gall bladder disclosed no lesions; gastric secretion was normal. A diagnosis of "gastric neurosis" having been made, the patient was sent home after 7 days. Within 2 weeks he returned to the hospital with the statement that he had been running a constant fever up to 105° F. During this 2 weeks' residence in the hospital, when his temperature was found to be elevated between 100° and 102° F. for no obvious reason (Fig. 62), he complained bitterly of feeling cold. He slept in flannel underwear and insisted on being covered with 12 blankets and having the door and windows closed. He was discharged from the hospital in an unimproved condition. After 3 weeks he was back at the hospital complaining of indigestion, weakness and constipation. He stated that his temperature, which he took daily, was between 101° and 103° F. During the first week of this residence in the hospital, his temperature remained consistently over 100° F., then swung between 99° and 100° F. for the next 2 weeks, at the end of which time he was sent home much improved. The pulse was consistently below the temperature level.

The fourth and last admission to the hospital occurred 1 year later (Sept. 23, 1932) when the patient returned because of insomnia, fever and anorexia. His temperature was 101.2° F., pulse 82 per min., blood pressure 160 systolic and 100 diastolic, and the respirations were 24 per minute. He was mentally confused and complained of extreme chilliness. *As on the previous admissions complete physical examination disclosed no abnormalities which could account for his abnormal*

signs and symptoms. All the laboratory data, including blood cultures agglutination tests for *B. abortus*, the typhoid and paratyphoid organisms, and stereo-radiographic examination of the chest, were negative. On October 3, sputum became profuse and signs of pneumonia were noted at the bases of both lungs. With this turn for the worse, the temperature began to rise, at first to about 102° F. and finally

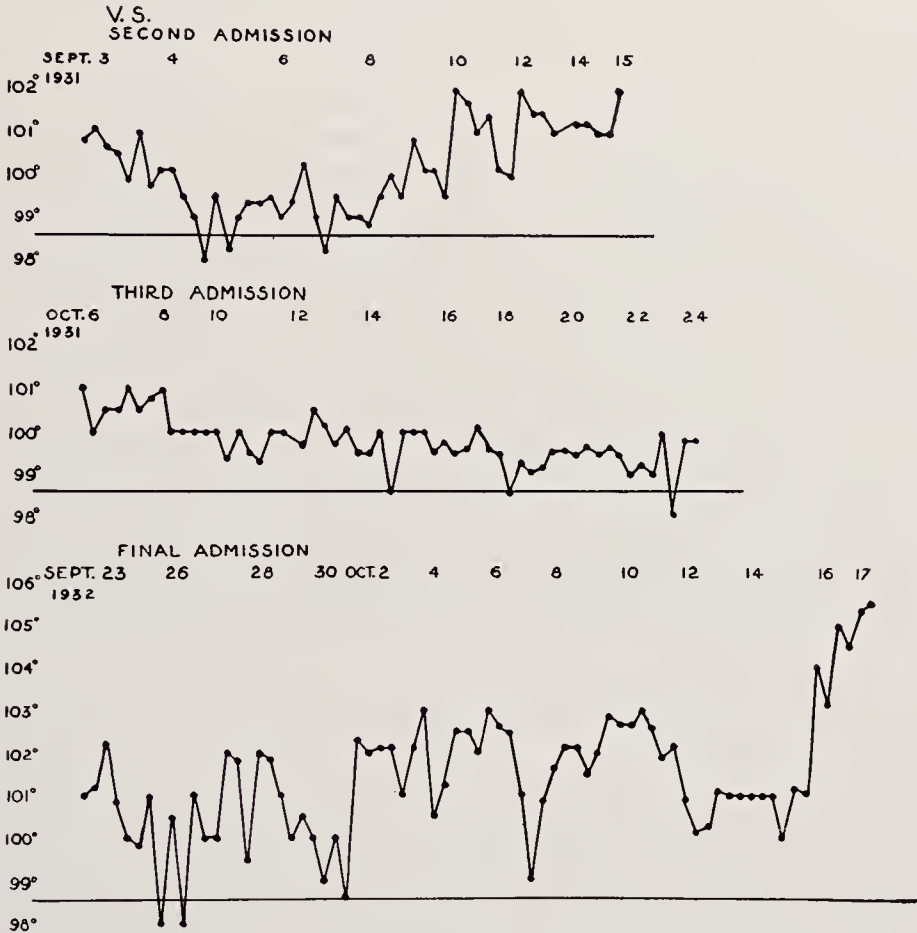


FIG. 62. Temperature chart of Zimmerman's case (1940) of hyperthermia. Note persistent hyperpyrexia during all three hospital admissions.

to 105.5° F. on the day of death, which occurred on October 17, 1932. During this last admission the daily fluid intake was watched and was always well below 2000 cc.

Necropsy. The only evidence of a recent inflammatory process was confined to the lower lobes of both lungs, where collections of polymorphonuclear leucocytes and fibrin were seen in the peribronchial regions and some of the alveoli contained small numbers of red blood cells.

Brain. A firm tumour mass of yellow color and somewhat oval shape was situated immediately behind the stalk of the pituitary gland and was attached to the right mammillary body (fig. 63). This tumour measured 8 mm. in greatest (trans-

verse) diameter. It was also adherent to the tuber cinereum but did not appear to invade this structure. Except for a mild dilatation of the ventricular system there were no further macroscopic lesions. The tumour lay ventral to the tuber cinereum immediately behind the infundibulum of the hypophysis, and seemed to be a part of the leptomeninges of this region. *It infiltrated the tuberal structures to the extent of destroying the ventromedial nucleus, and when followed posteriorly in serial preparations it appeared within the right medial mammillary nucleus. Most of the cells of the medial part of this mammillary body were replaced by the*



FIG. 63. Drawing illustrating small lipoma lying behind infundibular stalk and attached to right mammillary body in Zimmerman's (1940) case of hyperthermia. (Kindness of Dr. Zimmerman.)

tumour (fig. 63). Somewhat more posteriorly the entire right mammillary body, except for a narrow lateral rim of tissue, was replaced by the fatty tumour. The right mammillothalamic tract was interrupted by the growth, but the left tract was intact. With the disappearance of the mammillary bodies in the serial preparations, the fatty tumour occupied an extra-cerebral location, lying within the leptomeninges. None of the other hypothalamic nuclei or their fibre tracts were involved in any way. On the treatment of hyperthermia see Beaton, et al., 1943.

DIABETES INSIPIDUS. Human beings exhibiting abnormal thirst have been frequently described especially during recent years. With the thirst comes polyuria and hence the name "diabetes," which means literally "what passes through," *i.e.*, a siphon. It was early recognized that some people with polyuria had urine that was sweet to the taste and, in others, the urine was clear and insipid — "diabetes mellitus" and "diabetes insipidus." Prior to 1913, no treatment was recognized for diabetes insipidus; in that year Van den Velden found that commercial pituitrin

greatly alleviated the thirst of polyuria. Thus, in one instance, a boy of 18 had for a period of several months regularly passed between 15 and 18 litres of urine every 24 hours; on taking pituitrin 3 times a day, the polyuria was reduced to 2 gallons (Blumgart, 1922).

The fact that the thirst in polyuria tended to disappear under pituitrin therapy suggested that the primary disturbance might be in the pituitary itself. However, all necropsy evidence has been contrary to such a supposition, and, as indicated in the physiological discussion above, it has become clear that diabetes insipidus is produced by a specific lesion of the anterior nuclei of the hypothalamus. The work of Ranson and his collaborators has established that the supraoptic nuclei are primarily involved. Diabetes insipidus may exist as an isolated clinical symptom, especially in postencephalitic cases in which it sometimes persists indefinitely unaccompanied by any other signs or symptoms, save for personality change. With tumours of the hypothalamus, neighbourhood symptoms may appear, such as the adiposogenital syndrome.

ADIPOSOGENITAL SYNDROME. First recognized as a clinical entity by Babinski (1900) and Fröhlich (1901), the syndrome now, thanks to the work of Philip Smith and others, can be relegated to the middle group of hypothalamic nuclei, including the tuber and lateral nuclear masses. It is clear, moreover, that two discrete syndromes exist, one of adiposity and the other of genital dystrophy, since extreme adiposity may develop after encephalitis without regression of secondary sexual characters. In the adiposogenital syndrome in experimental animals and in human beings with suprasellar tumours, the two symptoms are generally seen together, and they no doubt result from disturbance of closely contiguous structures in the hypothalamic area. The syndrome differs from that produced by ablation of the anterior lobe of the pituitary, both in the presence of adiposity and in the fact that neither the thyroid gland nor the suprarenal cortex are affected. It also differs from that following primary removal of the pituitary body *in that affected individuals are singularly recalcitrant to hormone therapy*. Diabetes insipidus may be a complicating factor in the adiposogenital syndrome, especially when produced by an expanding tumour. With expanding tumours also, the adiposogenital syndrome may pass over before death into a state of cachexia and extreme emaciation (Fulton and Bailey, 1929; Bailey, 1940).

HYPERSOMNIA AND HYPOTHERMIA. As with the adiposogenital syndrome, two other quite diverse clinical symptoms frequently coexist,

namely, hypersomnia and hypothermia. All available evidence, both clinical and experimental, suggests that this is a syndrome of the posterior group of hypothalamic nuclei, including the mammillary body and the nucleus hypothalamicus posterior. Expanding tumours of this region tend similarly to bring on a state characterized by abnormal somnolence. Large lesions of this region also cause conspicuous fall in body temperature and cases with rectal temperature of 90° to 95° F. have been recorded. This obviously results from failure of the mechanisms of heat production. The heat loss mechanisms may also become impaired.

The subject of pathological disturbances of the sleep rhythm has a large literature of its own recently summarized by Harrison (1940). With tumours of the posterior hypothalamus, disturbances of sleep take many forms. There may be simple hypersomnia, a tendency to fall asleep at all times, often increasing in gravity and progressing to a state of continuous sleep. In these states of hypersomnia, signs of normal physiological sleep are present, namely, a constricted pupil, slow respiration, a slight fall in temperature, a diminished pulse and blood pressure, etc. During the early stages, the patient can be roused. There are also disturbances of the sleep rhythm which, however, are more often psychogenic than the result of an organic lesion (see Gillespie, 1929).

Ectors and Bailey have recently described 4 cases of tumours of the base of the brain, exhibiting a profound degree of hypersomnia which progressed to a state which they describe as "arrested consciousness." In one instance, a child with a glioma of the infundibulum, affecting the posterior hypothalamus, remained in such a state of arrested consciousness for 14 months, during which time she had continuously to be fed by a stomach tube. There was no increase in intracranial pressure. Dr. Bailey points out (unpublished) that no part of the brain is so notoriously prone to cause loss of consciousness, if handled, than the posterior hypothalamus and central grey of the aqueduct of Sylvius. Manipulation of the anterior hypothalamus, the cerebellum or cerebral hemispheres is less likely to cause loss of consciousness.

From the point of view of localization, it is as yet premature to associate temperature regulation or sleep disturbance with specific nuclei. Experimentally, destruction of the nucleus hypothalamicus posterior gives lethargy, fall of temperature, and generalized slowing down of all bodily functions; it is also associated with abolition or great reduction of primary waves in the electroencephalogram of the cerebral cortex (Obrador, 1943). The state of sleep produced by Hess in his experiments, however, is said to be the result of stimulation and not of destruction of tissue. It

would appear, therefore, that some focus exists in the hypothalamus, stimulation of which causes suppression of cortical activity. From the point of view of anatomical connections, the focus which one would naturally suspect would be the mammillary bodies, because of their heavy projection to the thalamic nuclei(cf. Harrison, 1940).

AUTONOMIC EPILEPSY. Symptoms of diffuse discharge of the autonomic nervous system in otherwise normal individuals have been described both for the sympathetic and the parasympathetic divisions of this system. Generally, however, there is some overlapping between the two divisions. Predominantly sympathetic seizures were described by Penfield(1929)in the case of small ball-valve tumours of the third ventricle, and Cushing(1932b)noted that parasympathetic outbursts occur in response to intraventricular injections of pituitrin and pilocarpine. They may be described separately.

Sympathetic epilepsy. Under the title "diencephalic autonomic epilepsy" Penfield relates the case of a woman, aged 41, who was subject to attacks with the following characteristics. In the middle of the night she would awaken and ask for cracked ice to relieve her fever. At such times, her face and arms were flushed a deep red, respiration became slow, tears rolled from both eyes onto the pillow, and she broke out into a profuse perspiration over her entire body. Saliva ran from the corners of the mouth, the eyes were open, the pupils large and bulbs protruded. The pulse became strong and rapid; gradually flushing faded, after which the pulse became weaker and slow. There was generally hiccoughing, followed by a brief period of shivering. Attacks similar in character to this were frequent, and towards the last few days of her life they became more severe. During one of them her respiration ceased. At autopsy, a small tumour was found within the third ventricle, which evidently acted as a ball-valve and the seizures were attributed by Penfield to a compression of adjacent nuclei in the third ventricle. No attempt was made to isolate the centres involved, but from experimental analogy one would anticipate that the lateral hypothalamic area and the posterior hypothalamic nucleus had been primarily disturbed(see Penfield and Erickson, 1941).

Sjöqvist(1941)has described a striking case of autonomic epilepsy in man associated with episodes of sham rage. It was characterized by simultaneous discharge involving the sympathetic and parasympathetic divisions. The lesion in Sjöqvist's case lay deep in the right temporal lobe and had caused marked distension of the third ventricle.

Parasympathetic attacks. In 1932 Cushing pointed out that when either pituitrin or pilocarpine were injected into the lateral ventricle of the human brain a dramatic response occurred within 2 to 3 minutes, characterized by a profuse drenching perspiration all over the body, except for any region of denervated skin such as was generally present over the cerebral bone flap. There was intense flushing of all normal areas of skin, a fall in blood pressure, increased peristalsis of the stomach and intestines, and within a period of an hour or two the rectal temperature might fall as much as 6° F. It was accompanied by a fall in basal metabolic rate sometimes as great as 20 points.

Cushing assumed that the pituitrin had acted upon some of the hypothalamic centres. As evidence he reported two cases in which large destructive tumours of the hypothalamus were present and in these no response was obtained to intraventricular injection. Similar parasympathetic discharge is evoked by intraventricular injection of acetylcholin (Henderson and Wilson, 1936); adrenalin injected in the same manner gives no response. Atropin abolishes all such drug responses immediately on intraventricular injection, evidently due to central action. Parasympathetic seizures of this character may occur also in cases of encephalitis lethargica. Such attacks, together with the drug reactions of Cushing, establish parasympathetic representation, but they offer little indication of localization.

SUMMARY

The hypothalamus is a phylogenetically old constellation of nuclei lying in the ventral part of the diencephalon just above the optic chiasm and sella turcica. It is the principal centre in the forebrain for integration of visceral functions involving the autonomic nervous system. The constituent nuclei may be divided into four groups: (i) anterior including the paraventricular and the supraoptic nuclei, (ii) the middle including the tuber, dorsomedial and ventromedial hypothalamic nuclei, (iii) the lateral area, and (iv) the posterior group including the posterior hypothalamic nucleus and mammillary bodies. Pervading the whole area are ill-defined neurons, grouped under the general heading of "substantia grisea centralis."

These nuclei have elaborate intradiencephalic connections. The mammillary bodies, through the tract of Vicq d'Azyr, have afferent and efferent connections with the anterior nuclei of the thalamus. The hypothalamic nuclei also have connections with the cerebral cortex, generally through secondary neurons via the zona incerta, septum pellucidum and the mammillothalamic tract.

Stimulation of the hypothalamus indicates that the posterior and lateral hypothalamic nuclei are concerned primarily with the sympathetic outflow, the following responses being seen: (i) cardiac acceleration, (ii) elevation of blood pressure, (iii) dilatation of the pupil, (iv) retraction of nictitating membrane, (v) piloerection, and (vi) inhibition of the gut. From the anterior and midline nuclei in the region of the tuber sweating is evoked, and bladder contraction, cardiac inhibition and increased peristalsis of stomach and intestines and bladder contraction.

Localized lesions of the hypothalamus indicate that destruction of the posterior nuclei and mammillary bodies causes a fall in metabolism, body temperature and heart rate, Horner's syndrome with myosis,

enophthalmos, ptosis, and a general state of lethargy akin to sleep. Cats also tend to become cataleptic. Destruction of the tuber region causes hyperglycemia, severe gastric disturbances, mucosal hemorrhages, gastric atonia, disturbed heat regulation and the adiposogenital syndrome. Destruction of the supraoptic nucleus, and of no other part of the hypothalamus, causes diabetes insipidus accompanied by degeneration of the posterior lobe of the pituitary and the nerve fibres in the neural stalk (hypothalamic parasympathetic outflow).

In addition to functional regulation of sexual activity, water, fat and carbohydrate metabolism, the hypothalamus is the primary centre of heat regulation. The posterior nuclei activate the mechanisms of heat production and conservation, while the dorsal part of the anterior group (specific nuclei undetermined) regulate the mechanisms of heat loss, including panting, sweating and vasodilatation. The hypothalamic nuclei are responsive both to reflex activation through the thermal receptors in the skin and to the temperature of the blood circulating through the region.

Five clinical syndromes of the hypothalamus are recognized: (i) *hypothermia* (posterior nuclei), (ii) *hypersomnia* (posterior nuclei and mammillary bodies), (iii) the adiposogenital syndrome with disturbed fat and carbohydrate metabolism (tuber cinereum), (iv) *diabetes insipidus* (supraoptic nuclei) generally accompanied by *hyperthermia*, and (v) *autonomic epilepsy* caused by tumours, infection or intraventricular drugs with manifestations varying with the site of the lesion and involving a mixture of sympathetic and parasympathetic actions.

The posterior hypothalamus contains predominantly sympathetic representation; the middle and anterior nuclei predominantly parasympathetic and the functions integrated clearly involve both systems; but all levels of the hypothalamus are subject to regulation from thalamic, striatal and cortical levels (ch. xxiii).

XIV

THE THALAMUS

HISTORICAL NOTE

"Thalamus" was the name given by Galen in *De usu partium* (Bk. xvi, 3) to those chambers at the base of the brain which were thought to supply "animal spirits" to the optic nerves. Literally, thalamus means an anteroom and hence the term *thalami nervorum opticorum* and the English equivalent "optic thalamus" were quite naturally derived. Galen's description of the thalami, however, leaves one in some doubt as to whether he was referring to the thalamic nuclei themselves or to the part of the lateral ventricles immediately overlying them. The thalami were more clearly described in the fourteenth century by Mondino, who called them "anchae" (buttocks), and later by Thomas Willis (1664), who adopted Galen's nomenclature and by this they have since been known. This function of the thalamic nuclei was little discussed and even in his thesis Stein in 1834 did not suggest that the thalami subserved general sensory functions. In 1865 the young French neurologist Luys described the major nuclei, including the "centre médian" (centromedian nucleus), and attributed olfactory functions to anterior thalamus, vision to anteromedial portion, audition to the lateral part of the thalamus, and somatic reception to his "centre médian." Gudden's (1870) contribution, that specific thalamic nuclei degenerate when certain areas of the cerebral cortex are destroyed, was another important landmark. This he recognized as a severe retrograde degeneration * due to interruption of axons of cells having their origin in the thalamus, and the phenomenon still is designated "Gudden's atrophy." This marked the beginning of the modern study of the thalamus. For full historical details Walker's recent monograph on the thalamus should be consulted (1938).

THE thalamus is the principal end station in the forebrain of the sensory systems of the body. Seven afferent tracts play upon the thalamic nuclei, *viz.*, the nerves of special senses: optic and auditory; and the somatic afferents: spinothalamic tract, dorsal trigeminal tract, medial

* Strictly speaking, Gudden's atrophy is more than that which we commonly associate with retrograde cell degeneration. Nissl, having at hand stains which showed the cellular structure of the neuron, was the first to describe retrograde cell changes. Gudden's method was to operate upon animals within a few days of birth and let them live varying lengths of time — some as long as 9 to 10 months. The changes in such cases are much more severe than those found following cortical extirpation in an adult animal surviving the operation 1 to 2 months. Even secondary and tertiary neurons may be affected. Nissl should be credited with first describing the retrograde *cell* type of degeneration, and Gudden's atrophy reserved for the more severe type which he described. The latter type of degeneration is now rarely studied. I am indebted to Dr. A. Earl Walker for this footnote and for assistance in the revision of the chapter for the 2nd edition. — J. F. F.

lemniscus (from the posterior columns), ventral trigeminal tract, and the cerebellar projections via the brachium conjunctivum. The olfactory, but not the gustatory, projections pass directly to the cerebral cortex. A third afferent source from the adjacent nuclear masses of the mesencephalon and hypothalamus is sometimes included, but these pathways are not yet well understood anatomically or physiologically. Recent investigation of the anatomical projections to and from the thalamus indicate that each of its major projections terminate, or take origin, in discrete and separable portions of the thalamic complex. It is, therefore, necessary to consider the anatomical subdivisions of the thalamus in the light of this work, particularly that of Le Gros Clark and of Earl Walker. In entering upon the subject, it is wise to recall the conviction of the late Professor Grafton Elliot Smith that the key to the interpretation of the cerebral cortex lies in an intensive study of the thalamus.

THALAMIC NUCLEI AND THEIR CONNECTIONS

Each thalamus in all primates, including man, is an ovoid mass, obliquely disposed and lying between the mesencephalon and striate bodies, completely overlaid by the cerebral hemispheres. It is a constellation of nuclei, each having a somewhat irregular shape, but all fitting into a three-dimensional mosaic which defies brief description. In the following account the terminology of Walker (1938) has been adopted. Anatomically there are six major nuclear masses: (i) nuclei of the midline, (ii) anterior, (iii) medial, (iv) lateral, (v) ventral and (vi) posterior groups (including pulvinar and geniculates). For various reasons, however, it is not desirable to follow a rigid anatomical scheme of exposition, since the nuclei can also be arranged in three major subdivisions in accordance with their anatomical organization and connections as follows:

Nuclei with subcortical connections made up of the nuclei of the midline, intralaminar nuclei, and the anterior ventral nuclei, all of which have entirely subcortical connections restricted to the diencephalon (thalamus, hypothalamus, subthalamus) and corpus striatum.

Cortical relay nuclei include those which receive fibres from the great sensory systems and project in turn to the primary motor and sensory regions of the cerebral cortex. These include lateroventral, posteroventral and anterior nuclei, as well as the geniculate bodies.

Association nuclei which receive no fibres from the ascending systems

but have numerous connections with other diencephalic nuclei, and project to association areas of the cerebral cortex, *e.g.*, parietal and prefrontal. These include the dorsomedial nuclei, lateral nuclei, and pulvinar. The nuclear groups will be described in this order.

NUCLEI WITH SUBCORTICAL CONNECTIONS. When a cerebral hemisphere is completely removed, the nuclei of the midline (paleothalamus), the centromedian nucleus of Luys, and the other intralaminar nuclei show no sign of retrograde cell degeneration; it is therefore assumed that they have no direct connection with the cerebral cortex (Walker, 1938). Save for the midline nuclei, the exact anatomical connections of this group are imperfectly known and few suggestions have been offered concerning their function, apart from the fact that they are probably connected with visceral activity and with intradiencephalic association.

Nuclei of midline. These nuclei are made up of ill-defined clusters of cells lying in the middle of the thalamus along the upper part of the walls of the third ventricle. In lower animals the cell masses are prominent, but in higher forms their function appears to have been replaced by the neothalamic nuclei (Le Gros Clark, 1932). Their connections take the form of finely myelinated fibres passing vertically downward to the hypothalamic and pretectal nuclei. In all there are five distinguishable groups, to no one of which has a definite function been assigned. Their names imply their approximate anatomical position. They are: *n. parataenialis*, *n. paraventricularis anterior*, *n. paraventricularis posterior*, *n. centralis medialis* and *n. grisea centralis* (fig. 64, 3 v).

Intralaminar nuclei including centromedian. Brief mention will suffice for these nuclei since their connections, entirely subcortical and principally intrathalamic, are virtually unknown. They include: *n. parafascicularis*, *n. paracentralis*, *n. centralis lateralis* and *n. centromedian*. The first three are small, but the centromedian is a much discussed nucleus which at one time was thought to project to the cortex; but this it clearly does not do. It has frequently been said to be the termination of the fibres from the trigeminal tracts or secondary gustatory fibres. Although a positive statement cannot be made to the effect that it receives no ascending trigeminal fibres, certainly few if any terminate in it, the majority ending in the *n. ventralis posteromedialis* (Walker, 1939). Fibres from the oculomotor nucleus and posterior longitudinal bundle approach it; many of these pass through without terminating in the nucleus. The nucleus is situated in the middle third of the thalamus and is surrounded by fibres of the internal medullary laminae within which it probably has developed; like the other intralaminar nuclei the centromedian has developed *pari passu* with the nuclei between which it lies. This has led Le Gros Clark to conclude that the centromedian and the other intralaminar nuclei are intrathalamic association centres. Walker (1938) reports that the centromedian degenerates when the globus pallidus is damaged, thus favouring the view of Papez and Rundles (1937) that it has important striatal connections (fig. 64B, CM).

Anterior ventral nucleus (n. ventralis anterior). The anterior part of the ventral nuclear group is relatively undisturbed by the removal of the cerebral cortex. That this part of the thalamus sends few if any fibres to the cerebral cortex is in keeping with its subcortical relationships. Ranson and Ranson (1941) have demonstrated in

the monkey that many fibres enter it from the globus pallidus by way of the ansa lenticularis and fasciculus thalamicus. The Vogts(1920)and Papez and Statler (1940) have also described this connection.

CORTICAL RELAY NUCLEI. The cortical relay nuclei have been the subject of more thorough study than any other part of the thalamus because of their relation to the afferent somatic projections and to the cerebral cortex. They include the anterior nuclei, the ventral(lateral and posterior), and the geniculate bodies; *all* these nuclei receive fibres from the ascending sensory systems, and their degeneration is practically complete when the cerebral cortex is removed. They may be described briefly as follows:

Anterior nuclei(fig. 64A). The anterior nuclear mass forms the tubercle of the thalamus, bulging into the lateral ventricle; it is composed of three distinct nuclei: anterodorsalis, anteroventralis and anteromedialis. The anterior group is relatively more conspicuous in lower forms than in the primates, since nuclei anterodorsalis and anteromedialis have regressed in primates. The demarcation between anteromedialis and anteroventralis is less precise in the higher primates than in the carnivora. In the chimpanzee the ventral part of the anterior nucleus is quite large while the other two are insignificant. These nuclei receive afferent fibres from the mammillary bodies and project to the posterior part of the cingular gyrus and to the paracentral lobule. As yet the discrete functions of the individual nuclei in the anterior group are unknown.

Ventral nuclei(fig. 64). The ventral group is made up of three principal nuclear masses, all of which, except the anterior ventral nucleus (already considered), degenerate when the cerebral cortex is removed. Anatomically, the ventral nuclei are bounded by the internal and external medullary laminae, the pulvinar and the lateral nuclei.

The projection of these nuclei to the cerebral cortex has given rise to dissension among investigators. Those experimenters(Le Gros Clark)using the retrograde cell degeneration method of Nissl have found a distinct antero-posterior arrangement of the projection, but those using Marchi degeneration(Sachs, Polyak, Crouch) or strychninization(Dusser de Barenne)have been unable to find such precise point-to-point projections. The solution of this riddle probably lies in the fact that the Marchi and strychnin method give maximum results, whereas with that Nissl technique degeneration cannot be appreciated unless at least 10 per cent of the cells are changed. For this reason the thalamocortical connections given below are the main or predominant projections, but do not preclude the possibility of other minor connections.

a. Lateroventral nucleus(fig. 64A, VL). This nucleus includes the anterior half of the ventral group, exclusive of the anteriorventral nucleus.

Its importance lies in the fact that it receives projections via the brachium conjunctivum directly from the dentate nuclei of the cerebellum, and sends projections to fields 4 and 6 of Brodmann — the motor area of the cerebral cortex. The principal connection with the cerebellum is

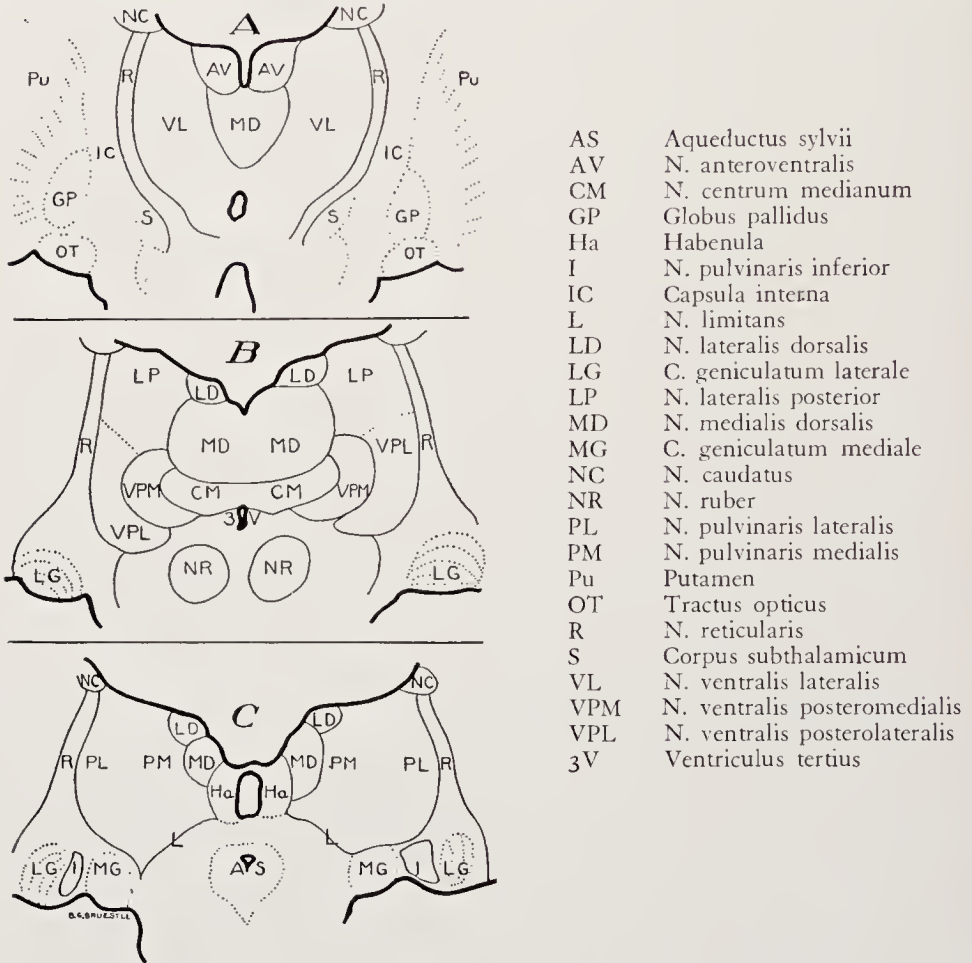


FIG. 64. Cross section of chimpanzee thalamus showing principal nuclear masses at three levels. (Camera lucida drawing by A. Earl Walker, 1938.) A, Anterior thalamus with anterior and lateroventral nuclei. B, Midthalamus with posteroventral and medial nuclei. C, Posterior thalamus with pulvinar and geniculate bodies.

contralateral, but it also receives a few ipsilateral fibres. Within the lateroventral nucleus itself there is also discrete topographical representation, *i.e.*, lesions restricted to the cerebral foot area (area 4a) cause degeneration in the lateral part of this nucleus, while arm area lesions give rise to degeneration in the middle of the nucleus, and face area lesions

to degeneration towards the midline(fig. 65). Whether there is any corresponding topical localization from the dentate projections remains to be determined.

b. Posterovenral nucleus(fig. 64B). The importance of the large posteroventral nuclear mass lies in the fact that it receives sensory projections from the spinal cord, posterior column nuclei and trigeminal nuclei, and sends projections to the postcentral convolution of the cortex (areas 3-1). The various projection systems impinging upon this nuclear mass end discretely, and form the basis of its subdivision into several distinct regions as follows:

N. ventralis posteromedialis(*Arcuate*; fig. 64B, *VPM*). This part of the ventral nuclear mass, sometimes known as the "arcuate" nucleus because of its semilunar shape, forms a crescent line lateroventrally from the centromedian; it receives the principal projections from the trigeminal nuclei and sends projections to the sensory face area of the cerebral cortex(areas 3-1; Sager, 1935; Clark, 1937). It is significant that this nucleus remains relatively constant in size throughout the mammalian series, whereas the more lateral parts of the ventral nuclei have developed immensely with increase in ambidexterity of the extremities, especially in the primates. The facial mechanism, including mouth, tongue, larynx, etc., which this nucleus subserves, is fairly even in complexity throughout the mammalian series, being somewhat more intricate in the primates.

Lesions in the region of the arcuate nucleus give rise to impairment of taste (Ruch, unpublished). Cortical lesions in the inferior portion of the precentral convolution have also caused a decrease in gustatory appreciation, and such experimental lesions cause retrograde cell degeneration in the medial part of the arcuate nucleus.

N. ventralis posterolateralis(fig. 64B, *VPL*). This is a large nuclear mass lying just lateral to the preceding nucleus, but the boundary between the two is not sharp; when stained for myelin, it is seen to be interwoven by two sets of heavily myelinated fibres, one passing towards the internal capsule and the other coming from the mesencephalon. Since this nucleus receives the fibres of the spinothalamic tract, as well as impulses from the posterior columns via the medial lemniscus, it forms a primary receptive field of the thalamus. It projects to the postcentral convolution(areas 3-1). Within the nucleus there is topical localization both in respect of the fibres it receives and of those it sends(fig. 65 *VPL*); thus the spinothalamic tract terminates somewhat more posteriorly and basally than do those of the medial fillet. The fibres from the gracilis nucleus end more laterally than those of the cuneate(Le Gros Clark, 1936d; Walker, 1938); in keeping with this, lesions of the sensory leg area of the cortex cause lateral degeneration in this nucleus, whereas lesions of the sensory arm area of the cortex cause degeneration more medially (Sager, 1933; Walker, 1934). Indeed, the lamination of the posterior columns appears to be preserved in the projections to the thalamus, and this spatial representation is further perpetuated in the cortical mosaic of sensory function. The spinothalamic and the medial lemniscus projections overlap somewhat, a fact of significance since both these tracts convey several modalities of sensation in common.

Lateral geniculate body (figs. 64-66, LG). In all primates the lateral geniculate body, a highly specialized laminated nuclear mass, forms a prominent structure on the posterolateral border of the thalamus. Each lateral geniculate consists of 6 laminae which are folded over the incoming fibres of the optic tract. The 2 ventral laminae are composed of large and rather deeply staining cells, whereas the 4 dorsal laminae are made up of smaller cells which stain less deeply.* Beneath the laminae

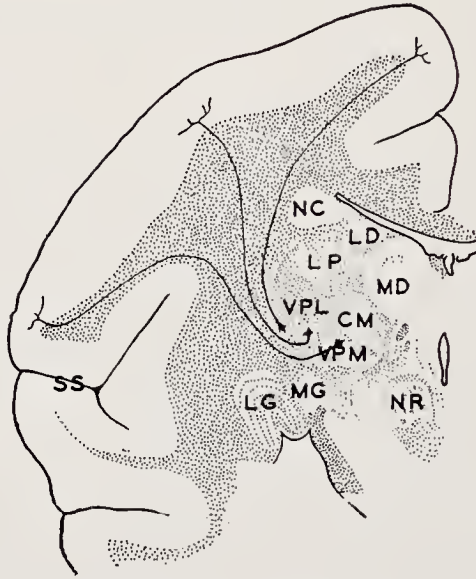


FIG. 65. Diagrammatic sketch of topical projections from ventral nuclei of macaque thalamus to post- and precentral convolution of cerebral cortex. VPM, nucleus ventralis posteromedialis; VPL, nucleus ventralis posterolateralis. For other abbreviations, see fig. 64 (Walker, 1938).

is the un laminated ventral portion of the geniculate body, a part which virtually disappears among the higher members of the primate series. The lateral geniculate body receives fibres directly from the retina, the fibres from the nasal half of the retina crossing in the optic chiasm; those from the temporal half remain uncrossed, the fibres from a given side interdigitating on successive laminae with fibres from the eye of the opposite side. The rostral third of the nucleus is concerned with periph-

* Le Gros Clark (1940) has suggested that this six layer arrangement is related to Helmholtz's color theory, the crossed retinal fibres passing to layers 1, 4 and 6 of the geniculate and uncrossed fibres to layers 2, 3 and 5. He believes that each conducting unit consists of three fibres related to sensations of red, green and violet in accordance with the Young-Helmholtz theory.

eral vision, the central region of the remaining two-thirds with macular vision (Brouwer and Zeeman, 1925, 1926; Le Gros Clark and Penman, 1934). From the geniculate there is a point-to-point projection to the striate area of the occipital lobe (cf. ch. xvii).*

Medial geniculate body (figs. 64-66, MG). The medial geniculate is an elongated nucleus which lies between the lateral geniculate body and the cerebral peduncles, and in primitive mammals forms a conspicuous rounded tubercle, bulging laterally from the caudal end of the thalamus. "The main part of the medial geniculate body of mammals is developed as a caudoventral extension of the main sensory nucleus of the thalamus, drawn out, it would appear, under the neurobiotactic influence of auditory impulses which pass up to it from caudal levels" (Le Gros Clark, 1933). It is composed of darkly staining cells, but is not laminated as is the lateral geniculate. As originally pointed out by Ferrier and Turner (1894), the medial geniculate receives projections by way of the lateral lemniscus from the cochlear nucleus, and thus serves as the principal thalamic focus for the reception of auditory impulses (ch. xviii). The detailed arrangement of these fibres in relation to the cochlea (Woolsey and Walzl, 1942) itself and with the cochlear nucleus has not yet been described. The medial geniculate projects to a small area of koniocortex in the temporal lobe along the inferior lip of the sylvian fissure (fig. 66). This is the auditory cortex (cf. ch. xviii).

ASSOCIATION NUCLEI. The association nuclei receive no fibres from the ascending somatic systems; they project, however, to the association areas of the cerebral cortex, notably the prefrontal lobes and the parietal regions. In this group there are three primary nuclear groups: the dorsomedial nucleus (MD), the lateral nucleus (LD, LP), and the pulvinar (PL, PM). These nuclei also have numerous connections with the cortical relay nuclei.

Dorsomedial nucleus (figs. 64-66, MD). This is a large nuclear mass which, like all the thalamic association nuclei, is best developed in man, diminishing progressively as one descends the phylogenetic scale. It receives few, if any, fibres from the ascending tracts, but establishes a rich connection with the lateral nuclear mass. The dorsolateral portion of this nucleus is made up of small cells, whereas the medial portion is composed of large cells. The large-celled region establishes connection with the hypothalamus by the periventricular system of fibres of n. and part of it projects to the orbital surface of the frontal lobe (Walker, 1940). Since this portion of the cortex is the cortical representation of the vagus nerve the hypo-

* Lorente de Nó showed that a strict point-to-point arrangement would be of no real value (ch. xvii).



FIG. 66. Diagram of thalamocortical projections. Areas with similar markings in thalamus and cerebral cortex(upper middle)have direct thalamocortical and, in many instances, corticothalamic connections. Abbreviations correspond with those of fig. 64 with following additions(Walker, *J. nerv. ment. Dis.*, 1937, 85, 254; see opposite page for abbreviations).

thalamic relationship of the magnocellular portion of the nucleus becomes meaningful. The small-celled portion has a large projection to the prefrontal region of the cerebral cortex (areas 9, 10 and 12 of Brodmann), and degeneration follows removal of the prefrontal region.

Lateral nuclei. There are two lateral nuclei: n. lateralis dorsalis (fig. 64B, LD) and n. lateralis posterior (fig. 64B, LP). The *dorsal* part of the lateral nucleus is situated just above the dorsal part of the medial nucleus; it is larger posteriorly than anteriorly. This nucleus, which increases markedly in the primates, receives a small projection via the fillet, but its principal connections are with the ventral nuclei, and it is thus to be regarded as an association centre developed from the ventral group. The *posterior* part of the lateral nucleus receives no projections from lower levels; its principal fibres come from the main part of the lateral nucleus and from the tectum, and as with the dorsal part of the lateral nucleus its functions are not well understood. A special region of the posterior part of the lateral nucleus is referred to as the pars angularis. The principal cortical connection of the lateral nuclei is with the parietal lobe exclusive of the postcentral convolution, which further supports the belief that it is primarily an association centre.

Pulvinar. N. pulvinaris is generally described as an outgrowth of the nucleus lateralis posterior and it appears relatively late in the phylogenetic history. Its increment is correlated with the increasing complexity of the supramarginal and angular gyri of the cerebral cortex to which it projects. Microscopically it is generally divided into lateral, medial and inferior nuclei, which together extend from the habenular complex to the caudal end of the thalamus. Le Gros Clark and Northfield (1937) in a detailed study of the pulvinar in the macaque find that the inferior part (fig. 64C, PL) projects to the parastriate area (area 18) immediately adjacent to the visual cortex, while the main part (medial nucleus, fig. 64C, PM) projects to the posterior sylvian receptive region adjacent to the auditory projection area. The pulvinar, therefore, is undoubtedly associated with visual and auditory integrations, but its actual connection with the primary subcortical visual and auditory centres has yet to be investigated. It receives no fibres from the ascending somatic tracts.

The principal divisions of the thalamus and the primary connections of its various nuclei are summarized in Table I on page 262.

THALAMOCORTICAL PROJECTIONS. The fibre systems from the thalamic nuclei to the cortex have already been mentioned in describing individual nuclei; certain general characteristics of these projections require

Abbreviations to figure 66:

AD	N. anterodorsalis	IS	Sulcus intraparietalis
AM	N. anteromedialis	OT	Tractus opticus
AS	Sulcus parieto-occipitalis	P	N. parafascicularis
CL	N. centralis lateralis	Pa	N. paracentralis
CS	Sulcus centralis	SN	Substantia nigra
EC	Fissura calcarina externa	SP	Sulcus precentralis superior
HPS	Sulcus precentralis inferior (upper limb)	SPo	Sulcus postcentralis superior
IF	Sulcus frontalis inferior	SS	Sulcus sylvii
IO	Sulcus occipitalis inferior	Su	N. submedius
IP	Sulcus precentralis inferior (lower limb)	TMT	Tractus mamillothalamicus
		VA	N. ventralis anterior

TABLE I. *The nuclei of the mammalian thalamus grouped on the basis of anatomical organization (for subcortical connections see text)*

SUBDIVISION	CONNECTION WITH ASCEND- ING SYSTEMS	NAME OF NUCLEUS	CORTICAL PROJECTION
I NUCLEI WITH SUBCORTICAL CONNECTIONS	Not known	Midline (paleothalamus)	None
		Intralaminar parafascicularis paracentralis centromedian	
	Globus pallidus	Anterior ventral	
II CORTICAL RELAY NUCLEI	Mammillary bodies	Anterior	Cingular gyrus
	Brachium conjunctivum	Ventral lateroventral (ventralis lat.)	Precentral gyrus (areas 4 and 6)
		posteroventral (ventralis post.)	Postcentral gyrus (areas 3-1-2)
		ventralis postero- medialis	face and neck
	Audito-visual optic tract lateral lemniscus	ventralis postero- lateralis	leg, trunk & arm
		Geniculate bodies lateral medial	Striate cortex Heschl's gyrus
III ASSOCIATION NUCLEI	None	Dorsomedial	Prefrontal region (areas 9-10-12)
		Lateral dorsal part	Posterior parietal (areas 5 and 7)
		Pulvinar	Peristriate and posterior temporal (areas 18 and 22)

brief mention. Perhaps the best known — those from the lateral geniculate body to the striate cortex of the occipital lobes — establish a precise relation between thalamus and cortex such that a small lesion of the striate area causes a predictable and correspondingly well localized retrograde degeneration in the geniculate body. Recent studies of other parts of the thalamocortical projection indicate that a scarcely less precise spatial organization exists between other thalamic nuclei and the cortical areas to which they project (fig. 66). Thus the posteroventral nucleus projects to the postcentral convolution (areas 3-1) in a mosaic

probably as precisely organized as the corticospinal fibres from the motor area; and the lateroventral nucleus projects similarly to area 4. Area 6 receives few fibres from the thalamus (fig. 67). The spatial organization between the dorsomedial nucleus and area 9 is also surprising, each anterioposterior plane of the nucleus projecting to a point on the cortex as in the case of the pulvinar.

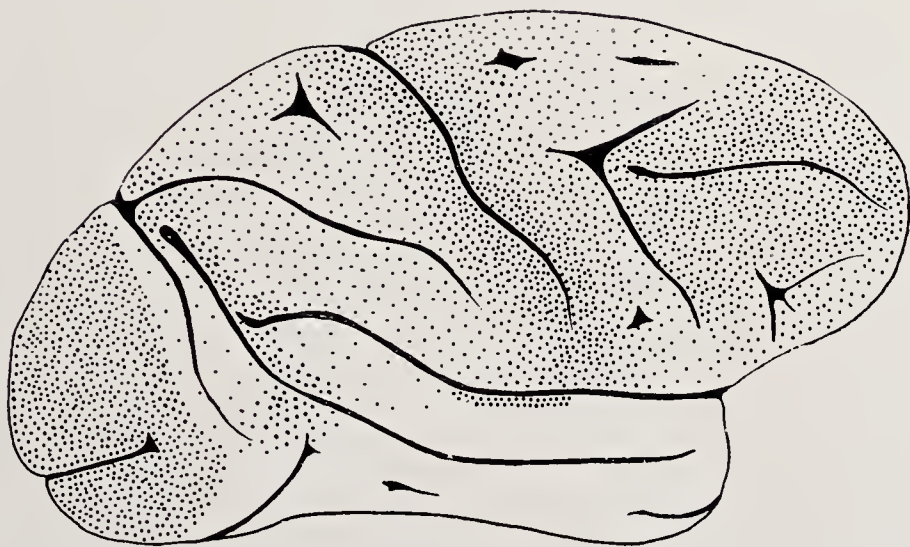


FIG. 67. Cerebral hemisphere of macaque showing relative density of thalamocortical projections to various regions of cerebral cortex (Walker, *Primate Thalamus*, 1938).

A three-dimensional diagram illustrating the principal thalamocortical projections of the macaque is given in figure 66. A left hemisphere is shown above and a series of sections of the left thalamus, beginning posteriorly with the pulvinar in the upper left corner and reading from left to right thereafter with more anterior sections. The cortical area to which a given nucleus projects is indicated by the same signs, *i.e.*, dots for frontal areas and dorsomedial nucleus, etc. Note that the posteroventral nucleus which projects to areas 3-1 is more posteriorly situated in the thalamus than the lateroventral which projects to areas 4 and 6. The key to the abbreviations is given in the legend to figure.

The relative volume of thalamocortical projection to the various cortical areas is indicated in figure 67. Note that the temporal lobe receives only the concentrated projections from the medial geniculate body and that the premotor and parietal areas also receive only a scant projection.

CORTICOTHALAMIC PROJECTIONS. Although known to von Monakow (1885), Cajal (1909) and others, the projections from cortex to thalamus have only recently been studied experimentally. D'Hollander (1922), using the Marchi technique, found evidence of discrete projections from given cortical areas to particular thalamic nuclei. Thus, from the striate cortex fibres pass to the lateral geniculate body with spatial organization similar to that exhibited by the fibres passing from the geniculate to the cortex (Biernond, 1929); * from area 19 a few projections pass to the lateral and ventral thalamic nuclei and a heavy projection to the pulvinar (monkey, Koikegami and Imogawa, 1936, p. 600). From the auditory cortex of the rabbit there is also a correspondingly precise projection to the medial geniculate body. Polyak (1932), Walker (1935), Sager (1933) and Hirasawa, *et al.*, have all made parallel observations in the monkey. From area 4 of the cortex Hirasawa and Kariya (1936) and Levin (1936) have traced fine fibres to the anterior part of the lateral and ventral nuclei (macaque); similar projections also arise in areas 1 and 2 (Uesugi, 1937). Mettler (1935) has found fibres from the "parietal lobe" and Sakuma (1937) from area 7 terminating in the lateral nucleus of the thalamus; those from the frontal eye fields (Hirasawa and Kato, 1935) and the prefrontal cortex pass to the dorsomedial nucleus. It is, therefore, evident that, in addition to receiving a spatially well-organized system of fibres *from* the thalamus, the cerebral cortex sends *to* the thalamus a system having, if not quite as precise, at least a distinct, organization. The significance of these projections will be discussed below.

SOMATIC SENSORY FUNCTIONS OF THE THALAMUS

In the sphere of sensation, the use of animals for experimental study is difficult and, for some problems, impossible, since an animal cannot describe its sensory perceptions; however, to certain categories of stimuli it "reacts" as would a human being, and inferences concerning perception may, in these circumstances, be justifiable. By training animals to discriminate between different weights, sounds, textures, etc., valuable evidence can be obtained about several sensorial capacities; and finally by the application of strychnine to sensory centres evidences of hyperesthesia may occur which are of value in the study of another group of sensory problems. But despite many ingenious experimental studies on animals, knowledge of sensory functions has until recently been drawn principally from human material—and from anatomical inference more than from experimental study.

Discrimination techniques have not yet been applied to study of somatic sensory functions of the thalamus. The general reactivity of animals to cutaneous and deep stimuli has been used as an index of thalamic function by many investigators, and the strychnine method has been applied with notable success by Dusser de Barenne and Sager (1931, cat;

* More recent work by Dusser de Barenne, *et al.*, Le Gros Clark and Walker have not confirmed the presence of a striato-geniculate projection. The cortico-geniculate fibres probably arise in the para- and peristriate areas.

1937, monkey). In interpreting thalamic functions it is first essential to distinguish between the activities of the cerebral cortex and those of the thalamus.

EFFECTS OF HEMIDECORTICATION. When one cerebral hemisphere is removed all of the cortical relay nuclei and the association nuclei entirely degenerate; those with subcortical connections remain. Such a procedure does not allow one to distinguish adequately between cortical functions and the functions of the relay nuclei, but it yields information of high significance. Thus during the first days following ablation of one hemisphere all modalities of sensation are virtually abolished on the opposite side of the body. This initial period of anesthesia is more profound and enduring in man and chimpanzee than in lower mammals (Walker and Fulton). After several days cutaneous responsiveness to pinching, pin-prick and other nociceptive stimuli returns, and eventually becomes well developed, but localization remains poor. Light touch, position sense and stereognosis are permanently abolished. Several cases of hemidecortication have been reported in man (Gardner, 1933; Dandy, 1933), with similar results. Thus, on the side opposite to the lesion, there ultimately returns appreciation of light touch, pin-prick over the face, as well as heavy touch and pin-prick, without accurate localization, over the body, but position and other forms of deep sensibility are forever abolished.

Two explanations have been offered of the effects of hemidecortication: either the thalamus, on the ablated side, is sufficient to account for these crude sensory capacities, or there is extensive ipsilateral representation in the uninjured thalamus. For the following reasons it is likely that both suggestions are relevant. In the first place, spinothalamic tracts (conveying cutaneous sensibility) are not entirely crossed, while the fillet fibres from gracilis and cuneate nuclei (conveying deep sensibility) do cross completely. In keeping with this, Foerster (1927) finds in man that unilateral section of the anterolateral tract for intractable pain often fails to give relief, whereas bilateral section of the tract will do so. In the second place, Dusser de Barenne and Sager (1931, 1937) met with symptoms of hyperesthesia on both sides of the body — most marked contralaterally — after injection of strychnine into the ventral nuclei (cat and monkey); this bilaterality of symptoms is seen, moreover, if strychnine is applied to the intact thalamus of a chronic hemidecorticate cat in which the opposite relay nuclei have degenerated. Walker and Fulton (1938) find similarly, *after removal of the second cerebral hemisphere of a chronic hemidecorticate macaque, that no response to cutaneous stimulation can be evoked for some days on the side opposite to this second ablation, whereas the ipsilateral side retains its response to pin-prick and heavy touch.* What other functions the thalamic nuclei which remain after decortication are capable of performing has not been determined; visceral stimuli are still localized, although somewhat crudely, by a hemidecorticate preparation, and it is therefore believed that these undegenerated nuclei are concerned principally with visceral sensation.

It is thus obvious that the exteroceptive field of the body surface is bilaterally represented in the thalamus, and that proprioceptive sensibility appears to have only unilateral representation. Further light concerning thalamic functions has been obtained through localized injury and stimulation of discrete areas in the thalamus.

LOCALIZED THALAMIC INJURY IN ANIMALS AND MAN. Localized injury of individual thalamic nuclei has been made by Clarke and Horsley (1905),

Roussy(1907), Sachs(1909)and others, for study of anatomical degeneration, but few observations are on record concerning the effects of such lesions on sensory modalities. In man, however, two groups of fairly well-localized vascular lesions are common: the first, that of the thalamogeniculate artery, whose occlusion generally destroys the posterior third of the ventral and lateral nuclei, was described by Déjerine in 1906, and there have been many subsequent cases(generally designated the "thalamic syndrome," Roussy, 1907). Disturbances of sensibility are severe in the upper and lower extremity on the contralateral side, but the face remains unaffected, a fact easily explicable on the basis of the medial position of n. ventralis posteromedialis which gives rise to the thalamocortical fibres for the face. With such lesions cutaneous sensation, although severely disturbed at first, generally improves, while deep sensibility remains permanently affected(*cf.* Riddoch and Critchley, 1937). These lesions are also frequently accompanied by severe hyperesthesias and paresthesias of the affected part(see below). Davison and Schick(1935, Case 6)have described a case in which the lesion(at the base of the ventral nuclei)had destroyed the termination of the spinothalamic tract and in this instance pain and temperature were alone affected. Clinically, apoplexy of the thalamogeniculate artery usually causes no disturbance of motor coördination, in spite of the severe sensory deficits just described.

The second vascular lesion common to the thalamus is thrombosis of the perforating artery, a branch of the posterior cerebral supplying deep structures in the anterior part of the thalamus; such an accident is generally followed by slight sensory changes in the contralateral extremity, and severe motor disturbances in the form of tremor, choreo-athetoid movements and ataxia. The anterior half of the lateral and ventral nuclei of the thalamus are involved as, not infrequently, is a part of the red nucleus, thus implicating cerebellar connections, but not the other ascending sensory systems.

Further studies on animals are needed following discrete nuclear lesions made with the Horsley-Clarke technique, as few have been undertaken since the well known paper of Sachs(1909; see Stavraky, 1936).

LOCALIZED STIMULATION OF THALAMUS. If a minute quantity(1 to 2 cu. mm.)of 2 per cent strychnine — with toluidine blue added for localization — be injected into the thalamus of cat or monkey, complex symptoms appear which vary in distribution with the site of the injection.

The symptoms include hypersensibility to all peripheral stimuli, together with spontaneous paresthetic disturbances of an unpleasant nature. The symptoms are most conspicuous when the ventral and lateral nuclei are injected; somewhat similar symptoms develop when the cat's medial association nuclei are injected. To quote Dusser de Barenne (1935, pp. 276-278):

"The sensory disturbances upon strychninization of one thalamus are present in the skin of both sides of the body, strongest on the contralateral side. In the deeper structures [*e.g.*, muscles] they are present only on the contralateral side."

"These experiments with Sager have established another fact, namely, the existence of functional localization in the thalamus. One finds there a face, arm and leg area. But in contrast with the subdivision of the sensory cortex, these thalamic areas for the three portions of the body are not sharply separated. On the contrary, they are rather widely overlapping. This expresses itself in the fact that usually the sensory disturbances are not localized only in either the face or the arms or the legs, but in the face and the arms, or in the arms and the legs and sometimes even are found present in all parts of the body. Only on strychninization of the most ventral portion of the ventral nucleus one finds the disturbances exclusively in the face, whereas the hindleg seems to be represented separately in the dorsal portion of the lateral nucleus [*ventralis posterolateralis*]. This overlapping of the various thalamic areas expresses itself also in the fact that sensory irradiation from arm to face and from face to arm has been observed in these experiments.

"Of importance for an understanding of the thalamic functions is the observation that the symptomatology on strychninization of the thalamus, at least in the cat, is the same after extirpation of the cortex of both hemispheres, even in the acute experiment, for it indicates the high level of functional integration attained in thalamic activity of the cat with regard to sensation."

Thus Dusser de Barenne and Sager (1931) corroborate in a general way the topical localization in the thalamus worked out through study of the thalamocortical projections. Hess and others have stimulated the thalamus faradically, but Hess' observations are not yet available for discussion in detail. Electrical stimulation of the thalamus may induce signs of hyperesthesia and paresthesia similar to that produced by strychnine injection.

GENERAL DISCUSSION OF THALAMUS

The thalamus can be discussed in relation to elementary sense modalities and to spatial localization of sensory phenomena. At any point below the level of the thalamus, a small lesion of the brain stem or spinal cord may, if appropriately placed, cause disturbance of one or more elementary forms of sensation. Above the level of the thalamus the individual sense modalities are no longer isolated and hence cannot be in-

dependently disturbed. In the thalamus itself there is overlapping, but not complete fusion of the sense modalities due to focal termination of the ascending somatic systems and also to bilateral representation in each thalamus.

Spatial representation of sensation as a whole is, however, sharply localized within the thalamic nuclei. It is thus possible for an individual finger to be affected by a small lesion of the cortex. Precise localization of this character would be unthinkable unless there was corresponding localization within all ramifications of the sensory system. In discussing the matter Walker(1938)remarks: "The sensory fibers from the leg convey temperature through the anterolateral tract, touch, vibration and position sense through the posterior columns and other proprioceptive modalities through the spinocerebellar system. All reach the lateral nuclear mass of the thalamus and terminate along its most lateral part juxtaposed to the reticular nucleus. From here cells project to the leg regions of the pre- and postcentral convolutions, thus maintaining throughout the entire system a definite spatial relationship. Undoubtedly the phenomena of local signs are closely related to this arrangement of the fibers from the bodily segments." Such considerations give meaning to the organization of the thalamocortical system. The significance of the corticothalamic projections is less clear and they have been the object of much speculation.

Head and Holmes(1920)suggested that the corticothalamic projection formed the anatomical basis of cortical inhibition of sensory phenomena; in the absence of this inhibitory influence excessive reaction resulted from sensory stimuli. The French school of neurologists and Kinnier Wilson(1927)in England, on the other hand, have pointed out that the severe paresthesias and hyperesthesias which often accompany thalamic injury are seen, not with cortical lesions, but with lesions of the thalamus itself(see Lhermitte, 1936, p. 89). They are therefore inclined to minimize the importance of these projections, and point out that hyperesthesia does not ordinarily accompany cortical ablations. Messimy and Finan(1938), however, have observed a moderate degree of sensory hyperactivity following bilateral lesions of the frontal areas of monkeys. Foerster(1927), supporting Head and Holmes, considers that inhibitory influence acts not only upon the thalamus, but also on a strio-thalamic system as well. Brouwer(1933)similarly believes that the projections provide a mechanism whereby the cerebral cortex can modify

the sensitivity of the primary receptive centres to render them more susceptible to incoming impulses. The corticothalamic projections, in other words, form a mechanism of "sensory attention."

In this connection one is reminded of the experiment of Amsler (1923) in which, while the cerebral cortex was intact in animals under light morphine anesthesia, stimulation of the sciatic nerve did not affect level of blood pressure or the rate of heart beat. When the cortex was removed, the same stimulus applied immediately afterwards caused sundry reflex effects including rise of blood pressure, inhibition of the heart, vocalization, etc. He interpreted his results as follows: When the cortex is intact, the pain pathways are "long-circuited" to the cortex for higher integration. When the cortex is removed, the impulses traverse phylogenetically older pathways through the thalamus. A similar interpretation of the corticothalamic projection has been offered by Dusser de Barenne (1935).

The extreme and often bizarre degrees of hyperesthesia and paresthesia which sometimes occur in the classical "syndrome thalamique" — in which the slightest stimulus may cause apparently excruciating pain — are difficult to account for. Most French neurologists have been inclined to attribute the phenomenon to local irritation of spinothalamic fibres as they enter the thalamus (see discussion of Davison and Schick, 1935); against this interpretation is the fact that the symptoms may persist unaltered for years following a vascular lesion affecting the ventral part of the thalamus. *Localized* release from intrathalamic association nuclei, possibly combined with release from cortical projections, appears a more likely explanation. The phenomenon does not occur following complete hemidecortication.

The somatic sensory functions of the thalamus are so conspicuous that its other sensory functions are sometimes lost sight of. Actually the somatic sensory functions are primarily mediated by only one nuclear mass, namely, the ventral; undoubtedly some of the association nuclei, such as the lateral and medial, play a part in these somatic integrations, but this leaves untouched the functions of the anterior, dorsomedial and midline nuclei, not to mention those of the pulvinar and geniculate bodies. The lateral and medial geniculate bodies, which are nuclei of special sense, will be considered in the chapters on the special senses which they subserve (ch. xvii and xviii).

The anterior nuclei remain something of a mystery. The anteroventral group, which become so conspicuous in anthropoid and man, convey impulses to and from the cingular gyri and the posterior hypothalamus, and therefore is presumably a relay station in the cortical integration of visceral functions and possibly of olfactory, but not gustatory sensibility. The anteromedial nucleus also projects to and from the cingular gyrus.

The dorsomedial nuclei, like the anteroventral, have attained their most extensive development in anthropoids and man, and their principal connection is with the frontal association areas. Various attempts

have been made to destroy the dorsomedial nucleus, but no recognizable symptoms have followed. Jacobsen and Walker (unpublished) destroyed these nuclei, believing that disturbance of immediate memory similar to that which follows bilateral ablation of the frontal association areas might develop following such a lesion; but they were unable to detect such deficit in trained macaques even after bilateral destruction. Strychninization of the medial nuclei gives rise to generalized symptoms of sensory overactivity, due presumably to the connections of the medial with the ventral nuclei. The midline nuclei have already been discussed above.

The pulvinar is an association centre primarily concerned with auditory and visual functions, but almost no detailed information is available concerning its activities. It may be concerned with stereognosis (ch. XIX).

THALAMUS AND CEREBRAL CORTEX. In an earlier section the difficulties of separating the functional activities of the cortex and thalamus were mentioned, and nearly all writers have emphasized the close functional relation between them (*e.g.*, Head and Holmes, 1911; Dusser de Barrenne, 1935). The cortex is essential for accurate discrimination of intensities and localization (*e.g.*, topognosis and two-point discrimination), and for such combinations of sensory capacities as are involved in the perception of spatial relations, *e.g.*, stereognosis, judgment of size, etc. On the other hand, large parietal lesions or even hemidecortication in both men and animals appear not to destroy the lower levels of sensory response. Nor does the disturbance from cortical lesions fall equally upon all sensory modalities. Pain and temperature sensibility suffer least impairment; light touch and muscle sense are most severely affected.

Even within the sphere of the modalities and levels of sensation that are peculiarly cortical it must now be recognized that in both animals and man a considerable compensation for large cortical defects is possible (cf. ch. XIX). But before such residual sensory function can be assigned to a functioning of the thalamus *independent* of the cortex, the great width of somato-sensory cortex must be considered. For example, the greater vulnerability of proprioceptive sensation over that of pain may mean not that the latter is a thalamic function but that it is unilaterally represented. At first sight it would seem that a study of the bilaterally decorticate animal would answer these questions. Such experiments, however, afford a clue only to the degree that the thalamus

has retained, in the course of phylogeny, the ability to function independently from the cortex; they tell nothing of the thalamic contribution in the integration of impulses relayed to the cortex, particularly by the association nuclei, nor do they accurately portray the extent of sensory function of which the thalamus is capable *when in receipt of impulses from the corticothalamic system*. Actually the function of the thalamus may, as the observations of Dusser de Barenne on strychnine

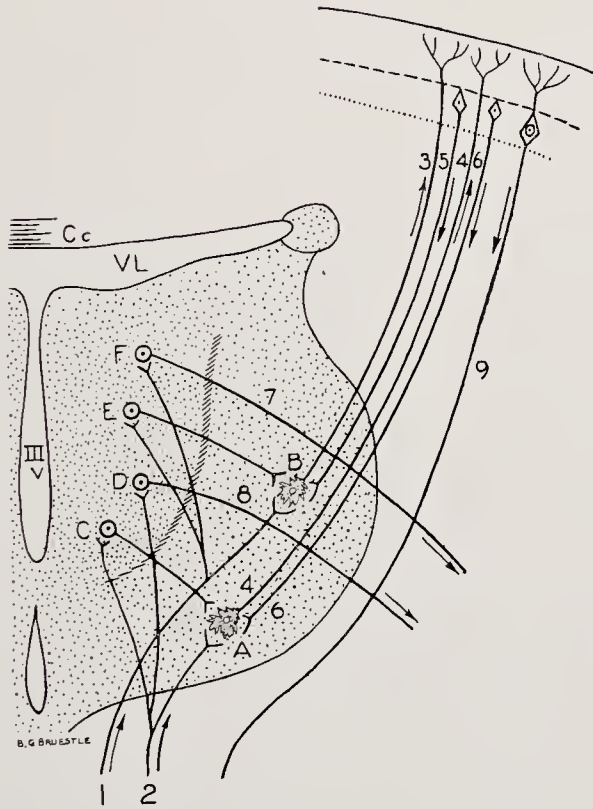


FIG. 68. Diagram showing interaction between thalamus and cerebral cortex as deduced from strychnine experiments of Dusser de Barenne (cat). Neurons A and B, and fibres 3 and 4 represent thalamocortical projections originating in lateroventral nuclei (fig. 65 VPL; these undergo retrograde degeneration after an appropriate cortical ablation). Corticothalamic neurons (5, 6) terminate among these cells. Since symptoms caused by strychninization of dorsomedial nuclei are unchanged by ablation of cortex, the medial group must receive afferents from other parts of the brain (fibres 1 and 2). These are represented as collaterals ending upon cells C, D, E, F, of dorsomedial nuclei. Since motor responses also occur from strychninization of medial nuclei of decorticate animal, motor neurons are represented (7 and 8) passing out to extrapyramidal mechanisms. Other connections are shown passing from dorsomedial nuclei to lateroventral (3 and 4). Neuron 9 is of corticospinal fibre of pyramidal system (Dusser de Barenne, *Res. Publ. Ass. nerv. ment. Dis.*, 1935, 15, 285).

stimulation and the anatomical studies of corticothalamic and thalamo-cortical projection suggest, subserve a high order of sensory function in addition to the more primitive aspects of sensation postulated by Head and Holmes.

Dusser de Barenne(1935, p. 285)has given an illuminating diagram of the corticothalamic relationship which is herewith reproduced in slightly modified form(fig. 68). The neurons represented are described in the legend. This scheme affords a basis to account for the hyperesthesia which occurs after strychninization of the medial association nuclei before and after removal of the cortex; the extra-pyramidal neurons on which the cells of these nuclei must act after decortication are also indicated. These connections would also account for the Amsler experiment. Further discussion of higher sensory integrations will be given in the section on the parietal lobes(ch. xix).

SUMMARY

The thalamus is made up of three groups of nuclei:(i)those with purely subcortical connections,(ii)cortical relay nuclei which transmit impulses from the great somatic sensory systems and from nerves of special sense to cerebral cortex,(iii)association nuclei which have no afferents save for their intradiencephalic and cortical connections. When the cerebral cortex is removed the relay and association nuclei exhibit almost complete retrograde degeneration, but those with subcortical connections remain undisturbed. The more important thalamic nuclei in each category with their principal connections are indicated in Table I on p. 262.

The thalamus has somatic, special sense and associative sensory functions: The *somatic* sensory functions are mediated by the ventral nuclei. The *lateroventral* portion receives cerebellar fibres and projects to areas 4 and 6 of the cortex. It is thus concerned with *unconscious* proprioceptive sensory data essential for motor movement. The *posteroventral* part with its two divisions, n. ventralis posteromedialis and n. ventralis posterolateralis, transmits exteroceptive and proprioceptive data from the spinal cord and trigeminal nucleus to the postcentral convolution. N. ventralis posteromedialis subserves the face and projects to the sensory face area(3-1); n. ventralis posterolateralis projects to the sensory arm, trunk and leg areas, each maintaining a discrete topical relation in their respective projections.

The parts of the thalamus concerned with *special* sense are the geniculate bodies and possibly the pulvinar. The lateral geniculates are concerned with vision, the medial geniculates with audition(and

possibly equilibrium), and the pulvinar with auditory and visual association.

The *associative* functions of the thalamus fall into two categories: (i) corticodiencephalic, and (ii) intradiencephalic. The corticodiencephalic associations are carried out by the so-called association nuclei, but the exact nature of these associations is not yet well understood, their general actions being inferred largely from their anatomical connections where these are known; thus the lateral nuclei play a part in somatic sensory integration of the post- and precentral convolution, the pulvinar in the special sense integrations of the parietal lobe, the dorsomedial and anteromedial nuclei in corticohypothalamic association, and finally the anteromedial possibly plays some part in olfactory associations of the cortex.

The effects of isolated destruction of the thalamus are described. Thus, destruction of the posterior third of the ventral nuclei causes transient impairment of cutaneous sensation on the contralateral side of the body and permanent disturbance of deep sensibility. Rupture of the thalamogeniculate artery often gives rise to such a lesion in man, and, in addition to causing the sensory symptoms just mentioned, hyperesthesia and severe paresthesia are prone to develop. Similar paresthetic disturbances can be produced by local injection of strychnine into the thalamus. Such strychnine injections have tended to confirm sensory localization obtained by anatomical methods.

The paresthesias and hyperesthesias which often follow thalamic injury are believed due to localized release from intradienecephalic and corticothalamic projections.

XV

CEREBRAL CORTEX: ARCHITECTURE, INTRACORTICAL CONNECTIONS, MOTOR PROJECTIONS *

HISTORICAL NOTE

Evidence of structural organization in the cerebral cortex was first noted by Francesco Gennari, an Italian medical student who, on February 2, 1776, found within the cortical substance of the human brain a white line most obvious in the occipital lobe. The "line of Gennari" is a reliable landmark of the primary visual cortex, the area striata. Vicq d'Azyr (1784) and Soemmering (1788) also observed Gennari's line, but it was not until 1840 that the French psychiatrist Baillarger demonstrated the white band to be composed of two bands separated by a thinner dark one (Fulton, 1937). These bands can be traced throughout the large portions of the cortex and have been called by modern authors "external and internal bands of Baillarger." The term "Gennari's line," which corresponds to the external band of Baillarger, has been reserved for the visual cortex. In recent years Elliot Smith (1907) has been able to divide the human brain into some fifty zones characterized by differences in Baillarger's dark and white bands. However, the modern era of research on the structure of the cerebral cortex may be said to begin with the Viennese alienist Meynert, who in 1867 systematically studied the cortical cells and established the fact that throughout the brain these cells are arranged in five horizontal layers. He considered two major divisions of the brain, which roughly correspond to what Kölliker called "rhinencephalon" and "pallium" and Vogt calls "allocortex" and "isocortex." The terms "archipallium" and "neopallium" have also been suggested, but as they are based on an ill-defined philosophical concept, they should be avoided. The allocortex has a white outer lamina and the isocortex a grey one. In 1874 the Russian histologist Betz discovered in the fifth layer of Meynert (human precentral cortex) the giant pyramidal cells which still bear his name. Several years later the English neurologist Bevan Lewis (1878) established the general existence of large pyramids in Meynert's fifth layer and suggested a division of the cortex into six cellular layers. Bevan Lewis' diagram was later adopted by Vogt and Brodmann, and has come into general use, although the designations of the layers have repeatedly been changed.

A great advance was made in 1891 by S. Ramón y Cajal. Golgi, the Italian neurohistologist, in 1886 had described the exact morphology of the pyramids and discovered that cells with short axons ramified within the cortex, *i.e.*, Golgi's type

* The first three sections (pp. 274-301) of this chapter have been prepared by Rafael Lorente de Nó. The extent of my debt to him will be obvious to those who peruse it. Dr. Lorente de Nó states in a letter: "One of the reasons why writing it has been so laborious is that I have verified in my collection of brain sections the truthfulness of every statement in the text and of every line in the drawings." Minor changes have been made in the second edition. — J. F. F.

II cells. His pupil Martinotti (see Cajal) had noted cells with axons reaching the plexiform layer. Cajal added the description of cells with horizontal axons in the first cortical layer, and in addition he discovered the afferent fibres of the cortex. All the essential elements of the cortex had then become known. Ramón y Cajal's observations were confirmed and substantially extended by the Swedish anatomist, Retzius who called the horizontal cells "Cajal's cells," and by the German anatomist, Kölliker who designated the afferent fibres "Ramón's fibres." Kölliker's account of the structure of the human cortex (1896) is one of the landmarks of neuroanatomy, and it marks the end of a historical period of research on the cerebral cortex. Between 1899 and 1902 Cajal made a thorough study of the finer structure of several regions of the human cortex, to which extensive reference will be made later. This led to the recognition of the structural differences between the pre- and postcentral convolutions of the human cortex.

At the beginning of the present century a new branch of neuroanatomy was created, *i.e.*, "architectonics." Its foundations were laid by Meynert, and by Hammarberg (1895), a young Swedish histologist working in S. E. Henschen's clinic, and by Cajal, the Spanish histologist; it is correct to state, however, that architectonics as such began with the independent work of Campbell in England and Vogt and Brodmann in Germany, all of whom made their first communications in 1903. Architectonics, let it be said in advance, is concerned, not so much with the structure of the cortex as with subdivision of the brain into regions of specific structure. Campbell's communications, presented by Sherrington to the Royal Society of London in 1903, were published in book form in 1905. He demonstrated that the human brain, as well as the brain of other primates, carnivora and ungulata, contains several regions of specific structure. In the human brain Campbell recognized some twenty regions and described the cellular — cytoarchitectonic — and fibrillar — myeloarchitectonic — structure of each region (figs. 69, 70).

The German school of architectonics at first did not lay great emphasis upon the plan of stratification. As indicated by the Vogts (1919, p. 300), Vogt and Brodmann, after careful study of the literature, selected a cytoarchitectonic diagram, which happened to be that of Bevan Lewis (*cf.* Brodmann, 1909, p. 15), to which the Vogts gave a myeloarchitectonic equivalent (see their fig. 19). These diagrams were for several years a tool by means of which first Vogt and Brodmann, and then their numerous associates, carried out extensive parcellations of the brain of man and of a large number of other mammals. Each one of the cytoarchitectonic layers or myeloarchitectonic zones was for these workers a place in which to look for structural variations. In 1909 the six-layer diagram of stratification acquired a new signification. Brodmann then stated that the diagram, up to that time a purely morphological concept, was based on an embryological moment. In the human embryo up to the sixth foetal month the cortex is unstratified, but soon stratification appears in the form of six alternately light and dark layers which are the same throughout the brain and, therefore, represent the fundamental type of stratification. Later on, differentiations take place in the various architectonic regions, either because some of the embryological layers decrease or disappear, or because one or more of them increases and becomes subdivided into sublayers. But no matter how deep the change may be, every adult stratum is derived from one of the embryological layers. Only in the allocortex was the six-layer plan never demonstrable, and according to Brodmann the allocortex was heterogenetic. This theory has been elaborated by the Vogts (1919) and Filimonoff (1929). Out of Brodmann's sweeping theoretical concept grew an ever increasing series of papers by numerous authors who tried to penetrate more deeply into the

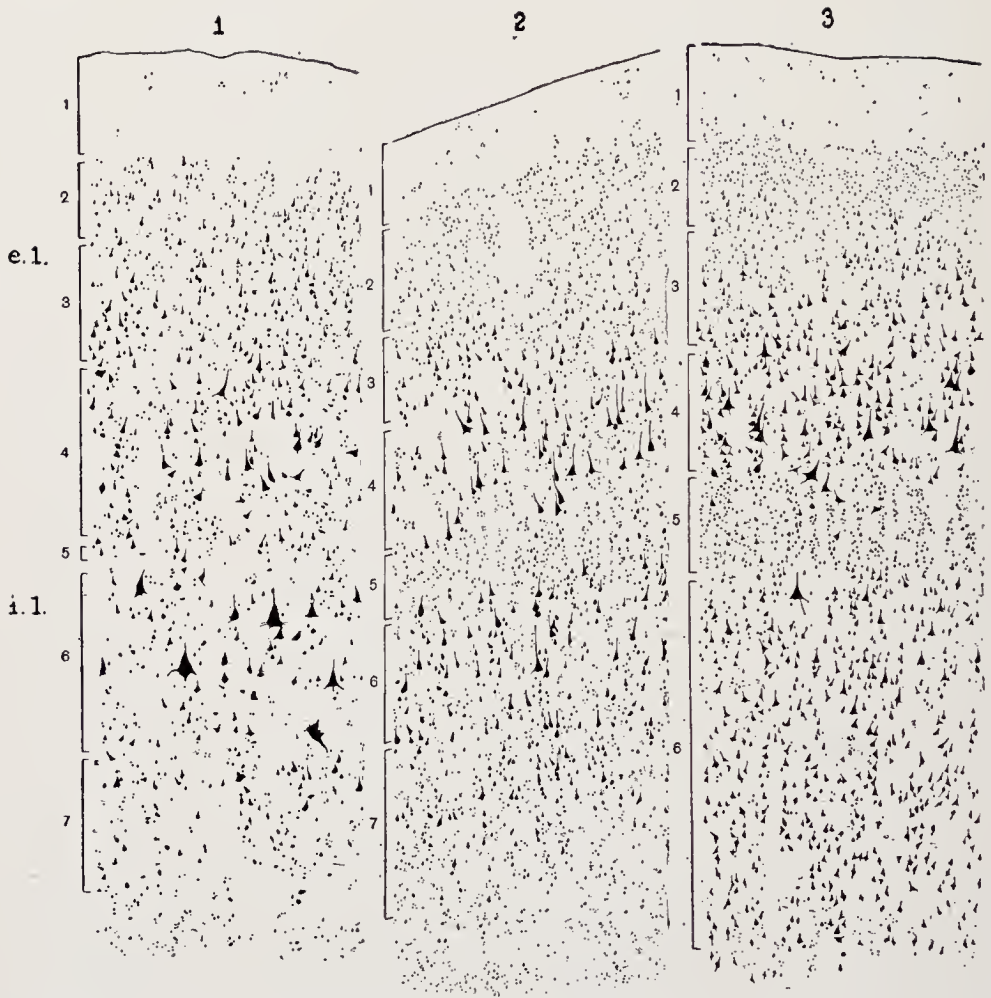


FIG. 69. Cytoarchitectonic pictures of representative areas of human brain. Only cell bodies are stained (Campbell, 1905).

1. *Motor cortex* (area 4 of Brodmann). Stratification (arabic numerals at left) suggested by Campbell does not agree with later established facts and is probably incorrect. Limit between external (e. 1) and internal (i. 1) laminae lies approximately at upper fourth of layer 4. This area is often called gigantopyramidalis from the presence of Betz cells. Its architectonic limits are, therefore, easily determined.

2. *Postcentral cortex*, near to wall of central sulcus (area 3 of Brodmann). Comparison of 1 and 2 reveals that without knowledge of structure of cortex, existence of two different areas can be ascertained. In fact, division was made despite a wrong concept of the structure of the precentral cortex.

3. *Temporal transverse cortex* (auditory of Campbell, probably 41 or 42 of Brodmann). There are striking similarities and differences between postcentral and temporal transverse areas; e.g., while stratification appears to be the same in both cases, thickness of layers, their densities, sizes and forms of cells, etc., are very different. No difficulty is experienced in distinguishing architectonic areas as different as these two. It is to be noted that Campbell did not distinguish between layers 6 and 7.

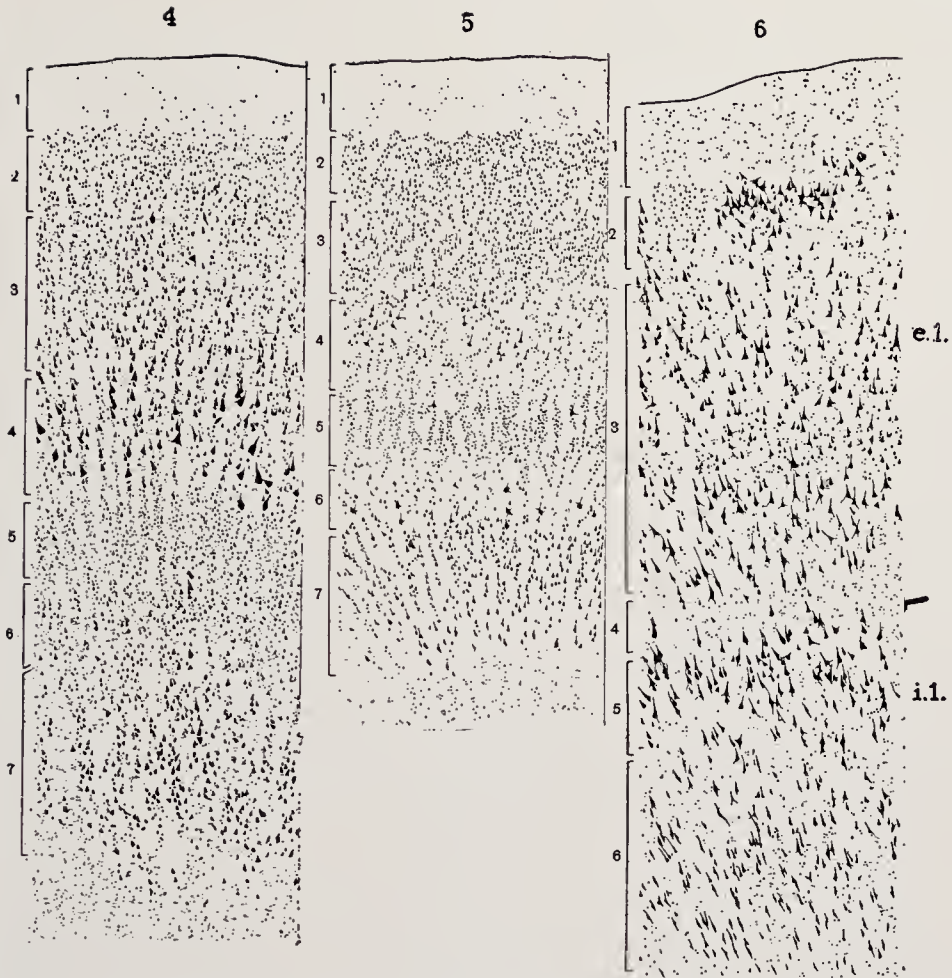


FIG. 70. 4. *Occipital cortex* (visuopsychic of Campbell, 19 of Brodmann). Campbell did not distinguish between layers 6 and 7, but approximate limit is indicated here. Note large size of pyramids in layer 4 (1va), and small size of pyramids of layer 6 (v). To distinguish between this area and temporal transverse or postcentral areas also offers no difficulty.

5. *Area striata* (visual of Campbell, 17 of Brodmann). This area is immediately recognized by small size of cells and appearance of (light) stria at middle of vertical section. This has often been interpreted as a duplication of a layer of granules (iv). Actually layer 4 (1va) is comparable to 4 of remaining occipital cortex. It must be noted that stratification at left of drawing is not as at centre, because there star pyramids are found at higher levels than at right.

6. *Cortex of lobus pyriformis* (28 or entorhinalis of Brodmann). The numbers of layers have a significance entirely different from that in drawings 2 to 5. For example, 4 is a layer of glia cells because at that level (cf. fig. 73, 11a) there are no nerve cell bodies but only a dense plexus of dendrites, axons and glia cells. Layer 2 corresponds to 11 in figure 75, 3 to 111, 4 to 111a, 5 to iv, and 6 to v and vi. Even if exact stratification of this area is unknown or misinterpreted, its architectonic boundaries can still be determined.

significance of the six layers. Studies of comparative anatomy made by Ariëns Kappers and his associates (1929) led to a complementary concept, namely, that the six-layer type was due to phylogenetic evolution of a primitive three-layer type, each layer having a primordial function. The enthusiasm evoked by Brodmann's concept overshadowed the factual information collected by a number of most reliable authors up to the time of publication of the books by Campbell (1905) and Cajal (1909). No more attention was paid to the fine structure of the cortex; studies on intracortical connections became irrelevant, and everything was explained in terms of the six- or of the three-layer diagram. Slowly but unfailingly these theoretical concepts dominated every line of research on the cerebral cortex and even experimental physiology has been deeply influenced by them. Thus it has come about that in one of the latest books on anatomy of the nervous system (Kappers, *et al.*, 1936) the intimate structure of the cortex is described in but a few words, although many pages are devoted to embryological and phylogenetic establishment of the six-layer diagram; but Brodmann's concept has proved to be based on faulty evidence (Lorente de Nó, 1934a). At the foetal stages at which Brodmann reported the absence of stratification, the cortex, when properly stained by the Golgi method, appears to contain the various specific types of nerve cells found in the adult brain. The cells of each type — pyramids, stars, spindles, cells with short axons or with ascending axons — are recognizable by their processes and by the position they occupy in relation to other cells. It is evident that at these embryonic stages the stratification is already definitively established and consequently that Brodmann studied only the final phases of differentiation. Therefore his observations have no direct bearing on the problem of elementary cortical organization. Moreover, the embryonic "light" layers correspond to zones of the cortex where the plexuses of dendrites and axons, which are not stainable by the Nissl method, are relatively better developed, so that the "dark" and "light" layers of the embryonic cortex do not coincide with the cell layers of the adult brain.

As forcibly stated by Cajal, the elementary pattern of cortical organization must be determined by means of intensive study of regions of specific structure, and this study should be carried out with the help of methods capable of yielding complete pictures of the cortical cell and fibres. Examination of the architectonic Nissl picture is only a first step in the analysis. The layers of cells found in the cytoarchitectonic pictures have been interpreted and labelled in many different ways. Even the authors of the cytoarchitectonic school have published most inconsistent descriptions, for although the layers have always been labelled according to the six-layer diagram, it often happens that equal denominations in two different photographs refer to entirely different systems of cells, in fact as different as a layer of nerve cells in one photograph and a layer of glia cells in another photograph (Lorente de Nó, 1934a).

At the present state of knowledge any plan of stratification suggested for the frontal and prefrontal isocortex is entirely hypothetical: but for

the parietal, temporal and occipital isocortex it is already possible to indicate a plan of stratification that is in agreement with the elementary pattern of cortical organization (figs. 71, 72, 73).

Stratification of parieto-temporo-occipital isocortex

External lamina	{	I (1). Plexiform layer,
		II (2). Small pyramids,
		III (3). Medium sized pyramids,
		IVa (4). Star pyramids,
		IVb (5). Star cells.
Internal lamina	{	V (6). Large deep pyramids,
		VI (7). Spindles.

Arabic numerals were used by Cajal and Campbell (fig. 69, 70), who differentiated a layer, their layer 4 of external large pyramids, which in this report is called a layer of star pyramids and must be incorporated into Bevan Lewis' diagram (1878a). However, since the latter has come into general use, the additional layer is designated IVa. It must be emphasized that the boundaries between layers, with the exception of the boundary between IVb and V, are never sharp, and that if they are ascertained with the help of only the architectonic picture are entirely hypothetical. Figures 69 and 70 show several drawings of the architectonic picture of representative areas of the human brain taken from Campbell's book. Although not as perfect as the photographs published by the German school, they clearly demonstrate the differences in cell size, density of the layers, layer thickness, etc., upon which the architectonic subdivision of the brain has been based.

GENERAL STRUCTURAL PLAN OF CEREBRAL CORTEX

Several structural features which repeat themselves throughout the entire cerebral cortex are likewise found in subcortical centres of higher complication, such as the quadrigeminal bodies, tuberculum acusticum, etc.: but many, if not all, cortical regions are characterized by specific structural traits that make it impossible to describe an elementary structural pattern which is valid for the whole cortex, unless after important simplifications the cortex is considered as a chain of neurons built on the plan of reflex arcs. How this can be done is shown in figure 74 and will be discussed in the following pages, but it is necessary first to investigate the actual structural plan of representative cortical regions. The study can be carried out in any cortical region of any mammal, but it is

facilitated by investigating the same region in various types of mammals and determining the structural traits that are common to all.

A number of cortical areas, although not many, can easily be recognized in all the mammals studied, *i.e.*, in mouse, rat, cat, monkey, and man. They are, for example, the primary visual cortex — area striata — which receives the optic radiation from the geniculate body: the area entorhinalis (Lorente de Nó, 1934a) which sends to Ammon's horn the powerful tracts described by Cajal; and the somatic sensory area which receives the thalamocortical projections from specific zones of the ventral nuclei. When any of these areas is intensively studied in different mammals, it is found that some of the structural details remain constant despite the variations in cell number, cell form and size, and the disappearance in the lower mammals of many types of cells found in the brains of the monkey and above all of man. *What remains constant is the arrangement of the plexuses of dendritic and axonal branches, i.e., of the synaptic articulations through which nerve impulses are transmitted.* This constancy is fortunate, because if it were otherwise studies made of the comparative anatomy and physiology of the cortex would have but a limited value. The semidiagrammatic drawings shown in figures 71, 72 and 73, which include representative types of cortical cells and fibres, are based on Golgi stains of the somatic sensory cortex of the mouse; but changes in the proportions of the drawings would make the diagram valid for the corresponding cortical regions of any other mammal, including man.*

Examination of the dendritic apparatus of the cells reproduced in the middle part of the drawing reveals how incomplete is the information upon which cytoarchitectonic research has based its far-reaching conclusions. The Nissl picture reproduced at the left in figure 71 gives approximate information about the form of the bodies of the cells, but

* It is scarcely necessary to emphasize that in the following description only the general features of cortical structure are considered. For example, the long pyramids (fig. 71, 7, 8, 9) will be viewed as a unitary type of neuron, while in fact, according to the distribution of the branches of their axons, they must be classified into several categories (Lorente de Nó, 1922). Likewise the specific afferents (fig. 71, *a*, *b*) are described as fibres of a single class, while they have been shown to include fibres with somewhat different distributions in the layers of the external lamina (1922, 1934a). These simplifications are permissible when the problem is that of ascertaining the elementary cortical pattern; but they should be avoided in study of the physiology of specific cortical areas. Exhaustive descriptions of cortical cells and axons have been published by Cajal (see complete bibliography by Cajal, 1909; Lorente de Nó, 1922, 1934; O'Leary, 1937, and O'Leary and Bishop, 1938).

leaves undescribed the distribution of the dendrites, which as a rule constitute by far the larger part of the synaptic surface of the neuron. On the basis of the architectonic picture, it is impossible to determine, for example, whether cells 14 and 15 (fig. 71) establish the majority of their synaptic contacts outside the layer in which their bodies are located, nor is it possible to differentiate between cells as radically different as 8 in figure 71, and 24 or 25 in figure 73. Cortical fibres are reproduced in figures 71, 72 and 73. While segments of them are myelinated, those segments which establish synaptic connections with dendrites or cell bodies are unmyelinated and consequently not stainable by the Weigert method. The myeloarchitectonic picture indicates the location of the myelinated segments of the cortical fibres, but does not give the slightest information about the zones of the cortex where the axons actually end.

The cortex has four main types of cells:

- 1) Cells with descending axons often reaching the white substance, to be continued by a fibre of projection or of association (figs. 72, 1 to 10, and 74).
- 2) Cells with short axons ramified in the proximity of the cell body, often within a homogeneous zone of the dendritic plexus (fig. 73, 21 to 25).
- 3) Cells with ascending axons ramified in one or several cortical layers (fig. 73, 18 to 20).
- 4) Cells with horizontal axons (fig. 73, 22).

The cortical neurons have synaptic connections with fibres of various kinds: afferent fibres, which are the axons of neurons coming from the thalamus (fig. 71*a, b, c, d*); association fibres, which arise in other cortical areas (fig. 71*e, f*); and intracortical fibres (figs. 72 and 73). In order to multiply the synaptic contacts, both dendrites and axons branch out repeatedly and form plexuses, the composition of which is indicated in figures 71, 72 and 73. Even a cursory examination of the distribution of the dendrites of the cells with descending axons (fig. 71) reveals the existence of a most remarkable arrangement, partly described by Cajal (1900-06) and first systematically analyzed by Lorente de Nó (1922, 1934*a*).

From the body of the cells arise several relatively short dendrites which may be called "basilar dendrites" and a long dendrite, the "shaft," directed toward the surface of the cortex. The length of the shaft is peculiar to each type of neuron. During its ascending course the shaft gives off collateral branches at levels characteristic for each type of neuron. Since the basilar dendrites are short and the collateral branches of the shaft are oriented chiefly in a horizontal direction, the result of

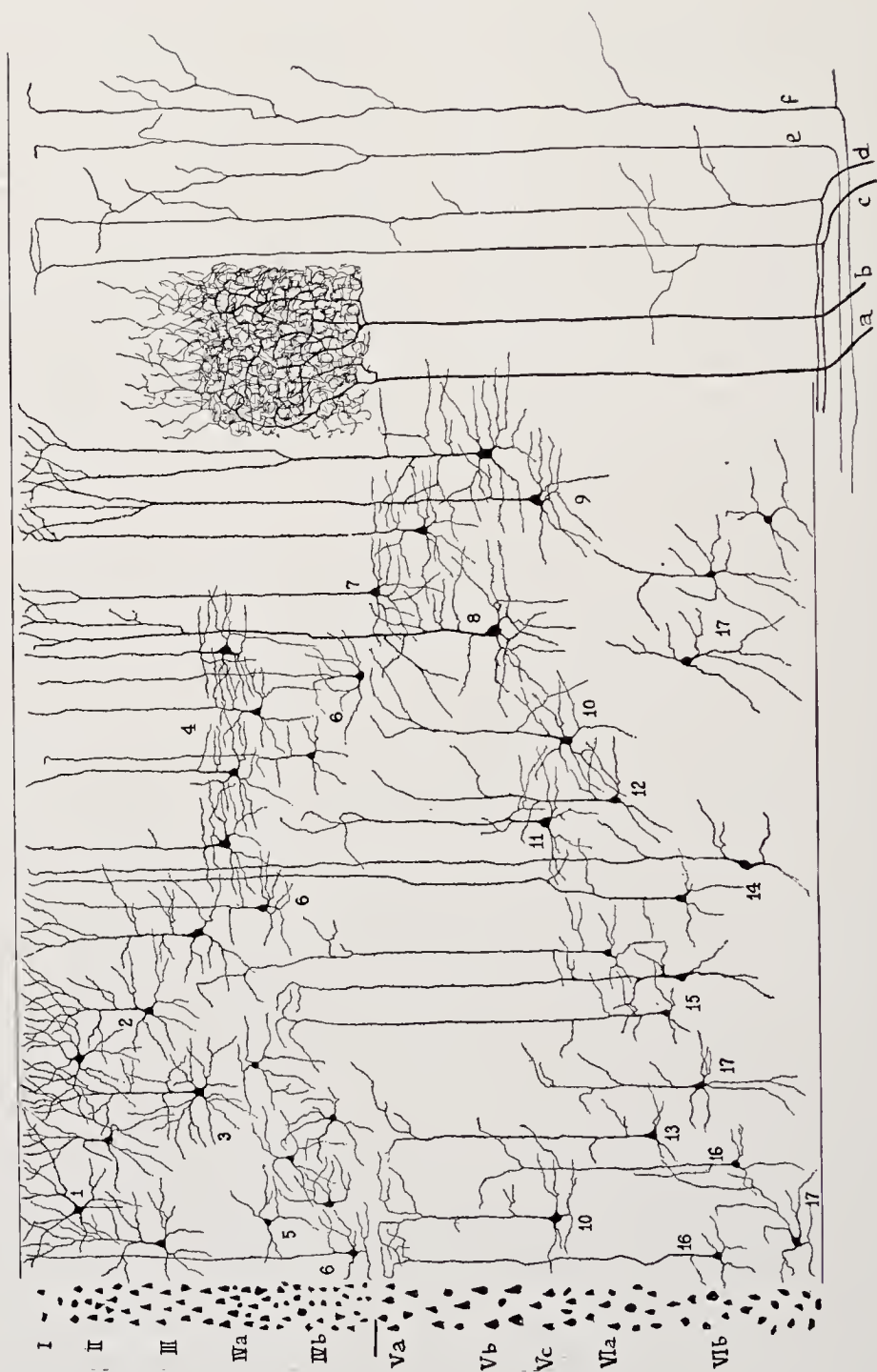


FIG. 71. Cortical afferents. For legend see bottom of opposite page.

the branching of the processes of the cortical cells is to fractionate the vertical section of the cortex into several strata of more or less horizontal dendrites crossed by vertical shafts. It is a remarkable fact: (i) that no two successive strata are articulated with the same fibres, and (ii) that each stratum contains dendrites from several architectonic layers. The cortical fibres of exogenous or endogenous origin run chiefly in a vertical direction, and by means of side branches establish synaptic contacts with dendrites or cell bodies of some of the zones of the dendritic plexus through which they cross (figs. 71, 74). The vertical fibres and their collateral branches form a plexus having as many strata as the dendritic plexus; each stratum has its specific composition. In some strata of the fibrillar plexus the collateral branches have a predominantly horizontal course and form the horizontal dark bands found in the myeloarchitectonic picture.

As indicated in figure 71, the cortex has been divided into six horizontal zones, each corresponding to a major group of strata of the dendritic plexus. These zones will be called "layers," and parts "sublayers" or "strata." The cell bodies represent but a small fraction of the dendritic plexus, and for this reason the cytoarchitectonic layers often have no immediate relation to the actual zones of dendritic and axonal plexuses.

LAYER I, the plexiform layer of Cajal, contains, besides horizontal cells (fig. 73, 22) and a few cells with short axons, the terminal bushels of pyramids and spindles of all the lower strata.

FIG. 71. At left side a diagrammatic Nissl picture of parietal cortex of adult mouse stained after Nissl. Cell layers are marked with Roman numerals. Except between ivb and va there is no sharp boundary between layers. At the centre, bodies and dendrites of representative types of cells with descending axons; to avoid complication of drawing axons have not been included (see fig. 72). At right the main types of cortical afferent fibres. 1. Pyramids of layer II; 2 and 3, pyramids of layer III; 4, large star pyramids; 5, star cells; 6, small star pyramids; 7, 8, 9, long deep pyramids; 10, short pyramids; 11, medium pyramids; 12, 13, short pyramids of layer VIA; 14, long spindles; 15, medium spindles; 16, short spindles; 17, deep star cells; a, b, specific thalamic afferents; c, d, unspecific or pluriareal afferents; e, f, association fibres. Cells have been reproduced from two consecutive sections through the brain of an adult mouse, stained after Golgi-Cox, and the fibres from section through brains of 11-day old mice stained after Golgi. In examining this drawing it must be considered that cells of each type appear at same level at more or less regular intervals, so that dendrites of all cells form a dense plexus, articulated with fibrillar plexuses such as that formed in layer IV and lower part of III by afferent fibres a and b. It must be noted that dendrites of cells of each type are distributed only through special zones of cortex, e.g., cells 5 have dendrites only in layer IV, cells 10 only in layer V and cells 17 only in layer VI, while other cells like 14 have dendrites in all layers. Cells with dendrites in several layers have a number of dendrites concentrated in one layer, e.g., the side branches of shaft and basilar dendrites of cells 4 are located in layer IV, those of cells 7, 8 and 9 in layer V, etc.

LAYER II, in addition to segments of the shafts going to layer I, contains the basilar and collateral dendrites of the small pyramids (fig. 71, 1).

LAYER III possesses pyramids (fig. 71, 2, 3) similar to those of layer II. Often, almost regularly, their shafts give off branches in layer II, so that no definite limit exists between the two layers. However, a division is advisable because branches

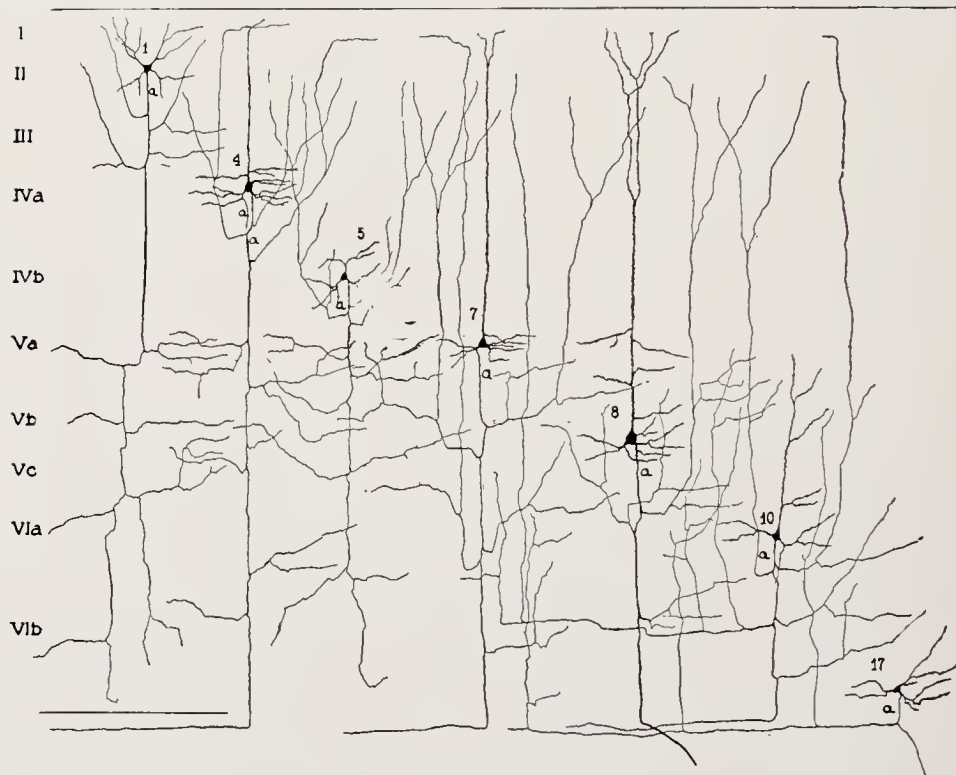


FIG. 72. Intracortical distribution of branches of representative types of descending axons. In order not to complicate drawing, branches have been omitted and others have been drawn shorter than they really are. The numbers on cells are the same as in figure 71. Note that collateral branches are concentrated in layers I-III and V-VI. Axons of cells 1 and 5 are entirely distributed within cortex although in higher mammals, especially in man, they may reach the white substance. Axons of cells 4, 7, 10 and 17 are fibres of association, and axon of cell 8 is a fibre of projection.

of the specific afferents (fig. 71, a, b) are in contact with dendrites, at least the basilar dendrites, of pyramids of layer III; but there are few, if any, pyramids of layer II that have basilar dendrites long enough to reach the zone of distribution of the specific afferents.

LAYER IV has two strata in which two main types of neurons are found, star cells (fig. 71, 5) with dendrites distributed entirely within layer IV, and star pyramids (fig. 71, 4, 6) which have shafts reaching the plexiform layer.* The star pyra-

* The division of the cells with descending axons of layer IV into star pyramids and star cells is of first importance. When this division was first made (Lorente de Nó, 1922), it was not realized that the large star pyramids form a distinct stratum in the upper zone of layer IV (sublayer IVa). This stratum has later been identified in the whole temporo-parieto-occipital isocortex, and it is important that it is present in the optic cortex of all

mids are distinguished (fig. 71, 4) from the ordinary pyramids by their shafts which have numerous horizontal collateral branches within layer iv, but none in layers ii and iii. After having given off its collateral branches the shaft usually becomes thinner and ascends to layer i, to end without branching or with a poorly developed bushel. The basilar dendrites of the star pyramids also run chiefly in a horizontal direction, in some cortical areas even exclusively so; but in other areas many of them descend toward the lower levels of layer iv, although without in general reaching the limit of layer v. The lower stratum of the fourth layer (ivb) contains both star cells with dendrites exclusively in layer iv and small star pyramids with thin shafts which reach layer i (fig. 71, 6). Layer iv is characterized by a dense fibrillar plexus formed by arborizations of the specific afferents. The boundary between layers iii and iv is not sharp, because some of the basilar dendrites of the pyramids of layer iii descend into layer iv; and especially in the cat, the shafts of some of the upper star pyramids may have one or two branches in the lower stratum of iii. The limit between layers iv and v is usually sharp, for at that level both the protoplasmic and the fibrillar plexuses suffer a radical change (fig. 71).

LAYER v in addition to the bodies of the classical pyramids (fig. 71, 7, 8, 9) contains the bodies of two other types of cells recently described (Lorente de Nó, 1934a), for which the designations of "medium" and "short" pyramids may be used. It is characteristic of the classical pyramids (7 to 9) to have a shaft which reaches the molecular layer, where it often ends by means of a complicated brush of branches, but at times remains undivided. It is also characteristic of these pyramids that not only the basilar dendrites, but also the collaterals of the shaft are distributed exclusively within layer v (Ramón y Cajal, 1900-06). When the cell body is located near the upper limit of layer v (fig. 71, 7), the shaft has no collateral branches; but if situated at lower levels (8, 9), the shaft has a number of collateral dendrites, none, however, passing beyond the upper limit of layer v.

The medium pyramids (fig. 71, 11) form an interesting type of cell. They have several dendritic branches in layer iv where their shafts end and therefore they have numerous synapses with the fibrils of the afferent plexus, almost as many as are found in the case of some star cells. The shaft of the short pyramids (fig. 71, 10) ends within layer v. Short pyramids are also seen in the upper part of layer vi (fig. 71, 12, 13). In fact, the limit between layers v and vi is not at all sharp. It is important to mention that layer v has three definite strata, the largest pyramids being found in the middle one (vb). It is not possible here to enter into the details justifying this division which, as will be seen later, may prove to be of high significance.

In LAYER vi are found three types of cells similar to the three types of pyramids mentioned above. The long spindles (14) have a shaft which gives off collateral dendrites in layer vi and then ascends undivided and without collaterals to reach

mammals studied, including mouse, rat, cat, monkey and man. Since Cajal did not identify it, he described the optic cortex as having a specific structure. The sublayer of star pyramids is present in area striata as well as in area peristriata. The sublayer of large star pyramids is called by the German architectonic school iva and ivb in the area striata, but iii in area peristriata. Both cortical areas when studied in Golgi stains show the same elementary pattern and stratification, the architectonic differences being due to the fact that in optic cortex the plexuses contain many more horizontal branches than in area peristriata. It is noteworthy that among the numerous plans of stratification described in the literature that suggested by Campbell (Plate xi, figs. 1 and 2) and reproduced here in figure 70, 5 is the only one that is strictly correct.

layer I. The shaft of the medium spindles (fig. 71, 15) ends in layer IV within the plexus of specific afferents. Finally the short spindles have a shaft ending in layer V (fig. 71, 16). In layer VI there are also a number of cells (fig. 71, 17) with dendrites distributed exclusively within the limits of their own dendritic stratum; these may be called deep star cells. A division of layer VI into two sublayers (via, vib) is from many points of view necessary, but for the purpose of the present report it may be disregarded.

CORTICAL AFFERENTS. The main types of the afferent fibres of the cortex have been represented on the right side of figure 71. A number of branches have been omitted in order not to complicate the diagram excessively. Some of the fibres (*a, b, c, d*) come from the thalamus (thalamo-cortical projections), and others (*e, f*) from cortical regions (intracortical association fibres). Fibres *a* and *b* represent the specific afferents: for example, the fibres coming from the external geniculate body to the visual cortex, those from the internal geniculate body to the acoustic cortex, the fibres from the thalamic relay nuclei to the somatosensory area, etc. They ascend myelinated and undivided through layers VI and V, and, having once arrived at layer IV, divide repeatedly into numerous branches, forming a plexus located chiefly in layer IV. Some branches ascend still farther to layer III where they form a much less dense plexus.

It is evident that although the cells of layer IV have the greatest number of *synapses* with specific afferents, many cells of other layers also have such synapses—for instance, the long pyramids (fig. 71, 7, 8, 9), the long spindles (fig. 71, 14) in their shafts, and the medium pyramids and medium spindles (fig. 71, 15) in the terminal bushel of their shafts. But the short pyramids (fig. 71, 10, 12, 13), the short spindles (fig. 71, 16), and the deep star cells (fig. 71, 17) have no synaptic contacts with the specific afferents. There is no doubt that the latter categories of neurons are stimulated by impulses resulting from cortical activity, through impulses carried by the unspecific afferents (fig. 71, *c, d*), or by association fibres (fig. 71, *e, f*).

A second type of afferent is represented in figure 71 by fibres *c* and *d*, which are of thalamic origin and innervate at least two adjacent cortical fields. Whether this type of afferent is present in all cortical areas is still unknown; in the mouse, these afferents have been found in several specific areas, but their existence has not been verified in higher mammals. Their ultimate destination is unknown, but it has been established that during their course in the white matter they give off collaterals ascending into the cortex and reaching as far as layer I. During their ascend-

ing trajectory the collaterals give off branches at all levels of the cortex, but chiefly in layer VI.

A third type of afferent is found in the association fibres(*e, f*) which come from other cortical areas, from either the same or the opposite hemisphere; in the latter case they are called callosal fibres. The association fibres give off collaterals in the deep layers, especially VI; but their main territory of distribution is in layers I to IV, and especially II and III. As will be seen presently, the interareal association fibres(*e, f*) have a distribution similar to many of the collaterals of the descending axons(fig. 72); this indicates that when a cortical cell discharges impulses into its axon it must modify the activity of the cells in the area in which it is located in a way similar to that in which the activity of the cells of other cortical areas or even of subcortical centres is modified.

CORTICAL EFFERENTS. Representative types of cortical descending axons have been reproduced in figure 72. It may be seen in the semi-diagrammatic but otherwise accurate drawing that the cortical axons, without exception, even when they leave the grey matter to form fibres of projection(fig. 72, 8) or of association(fig. 72, 4, 7, 10, 17) have an extensive intracortical arborization. Since the impulse conducted by a fibre necessarily passes into its collaterals and branches of the descending axons are distributed in the same territories as the cortical afferents, there can be no doubt that the effect of the impulses entering the cortex depends largely upon the impulses at that moment circulating through the descending axons as a result of the existing cortical activity. The intracortical distribution of the axonal branches is as systematic as that of the dendrites; again there is a sharp difference between layers I to IV and layers V and VI.

The axons of the pyramids and star cells of LAYERS I TO IV(fig. 72, *a* of neurons 1, 4, 5) have their ramifications chiefly within the grey matter, although a number of axons of pyramids, especially of the large star pyramids, reach the white substance and form association and callosal fibres. During their descending trajet they give off a number of collaterals; the initial branches are poorly ramified recurrent fibres distributed among the fellow pyramids, chiefly among those located at higher levels. It is a remarkable fact that layer IV receives but few collaterals from the axons of the pyramids of layers II and III, although the axons of the cells of layer IV have collaterals in that layer. Once arrived at layer V, all the pyramidal axons give off a great number of more or less hori-

zontal branches, distributed throughout layers v and vi, but especially in the upper part of v.

The axons of the pyramids of LAYER v are as a rule continued by efferent projection(fig. 72, 8) or association(fig. 72, 7) fibres. It is noteworthy that the short pyramids located(fig. 72, 10) in layer vc and in the upper stratum of layer via form one of the main sources of the callosal tracts. The axons of the spindles of layer vi also often reach the white substance to form a fibre of association. Likewise the deep star cells(fig. 71, 17) of layer vi give rise to association fibres, chiefly those which after a short course through the white matter again penetrate the cortex, *i.e.*, the U fibres.

All the axons of LAYERS v AND vi without exception have several repeatedly branched collaterals, a number of which remain in layers v and vi where they constitute a rather dense plexus of chiefly horizontal fibres; but in addition, many of these axons have one or more recurrent collaterals which, usually myelinated, cross through layers v and iv to reach layers iii and ii where they branch out and end among the pyramids of those layers, or even ascend to layer i.* It is significant, as first established by Cajal, that in some cortical fields the recurrent collaterals of the small pyramids of layers va and vc(fig. 71, 7, 9) and of the spindles of layer vi(fig. 71, 14, 15, 16) are the most important parts of the axonal apparatus, for the reason that they are thick and the axon does not reach the white substance(cf. Lorente de Nó, 1934a, fig. 5). A glance at figures 71 and 72 reveals the great importance of the system of collaterals of cells with descending axons. The fibrillar plexus of layers v and vi is chiefly composed of their branches and, what from a theoretical point of view is even more important, the fibrillar plexus of layers ii and iii receives the great bulk of recurrent collaterals from the axons of the cells of layers v and vi. Layer iv has but few collaterals coming from descending axons other than the axons of its own stars and star pyramids, and even those collaterals usually ascend to layers iii, ii and i where they end. Although the system for intracortical conduction of impulses formed by the branches of the afferent fibres and of the descending axons is a

* In lower mammals collaterals of descending axons have but short horizontal trajects in the strata of external lamina, but in higher mammals, especially in man, horizontal trajects are long and form powerful horizontal striae of myelinated fibres which have received various designations in myeloarchitectonic descriptions. They help to fractionate the external lamina into substrata which in cytoarchitectonic descriptions are termed *IIa*, *IIb*, *IIax*, *IIb*, etc. Since these substrata vary from field to field the designations have a different signification each time, and their value is therefore only "geographic."

powerful one, it is almost overshadowed in wealth and complexity by the plexus of ramifications of the short and ascending axons.

NEURONS WITH SHORT AXONS. There are many types of cells with short or ascending axons, in fact they constitute a considerable part of the cell population of the cortex — the larger the number, the higher is the brain in the series. As already stated, these cells may be classified into three main groups: *

a) Cells of the classical type II of Golgi with rather short dendrites which often extend through only one zone of the dendritic plexus (fig. 73, 23 to 26). The axonal arborization is distributed approximately in the same territory that is covered by the dendrites. Cells of this type are found in every cortical layer or, better said, in every stratum of the cortical plexus. Thus, cell 23 lies within the plexus of layers II and III, cell 24 in layer IV, cell 25 in layer V although chiefly in Va, and cell 26 in layer VI. It is an important fact that these axons (fig. 73, 24, 25) may form baskets enveloping the bodies of the pyramids and other cells with descending axons, so that the discharge of the cell with a short axon results in powerful, practically simultaneous stimulation of a large number of other cells.

b) Cells with ascending axons (fig. 73, 18 to 20) are also found in every cortical layer; their dendrites are sometimes distributed within one layer (fig. 73, 18, 21) but frequently they cross several layers (fig. 73, 19, 20). These axons in some cases form dense arborizations similar to those of the short axons (fig. 73, 18, 19, 20), but in other cases their arborization is lax (fig. 73, 21). There are ascending axons distributed through many layers, and axons with the arborization concentrated in one layer. Thus the axon of cell 21 is distributed in layers II to VI, and that of cell 18 gives branches to layers I, II, III, V and VI, but does not establish contacts within layer IV. The axon of cell 19 has a dense arborization in layer IV and gives but few branches to the upper layers. Finally the axon of cell 20 is rather uniformly distributed through layers I to IV. It is an immediate consequence of the existence of cells with ascending axons that when the cells of the upper layer with descending axons stimulate the cells of the deep layers, volleys of impulses are sent back to the upper layers. For example, when a discharge of the star cells causes the pyramids of layer V to respond, cells such as 19 will send impulses back to the layer of star cells; similarly cells such as 18 will send impulses to layers II and III.

c) The cortex also has cells with horizontal axons, the most conspicuous type being the horizontal cells of layer I (fig. 73, 22); their axons run for long distances, establishing contacts with the shafts of the pyramids and spindles of layers II to VI. In the same class belong cells with short axons which have their axonal arborization in the same layer where the body is located but at some distance from it, so that the impulses carried by their axons are delivered to cells with descending axons not reached by the same fibres which stimulate the short axon cell (fig. 75, 5).

* In the following paragraphs an attempt is made to systematize the description of the cells with short axons. It has been customary (cf. footnote on p. 294) to divide these cells into types according to layers in which the bodies are located. This procedure, justifiable from one point of view, leads to the differentiation of an excessive number of cell types, since similar cells distributed through several layers may be described as belonging to several different types. However, it must be noted that within the three main classes considered in the text, several specific types distributed through one or several layers can be differentiated.

INTERACTION BETWEEN NEURONS. It is possible now to reach a comprehensive view of the organization of the cortex. The small strip reproduced on the left of figure 71 is the vertical section of a cylinder having a specific afferent fibre like *a* as axis. All the elements of the cortex are represented in it, and therefore it may be called an *elementary unit*, in

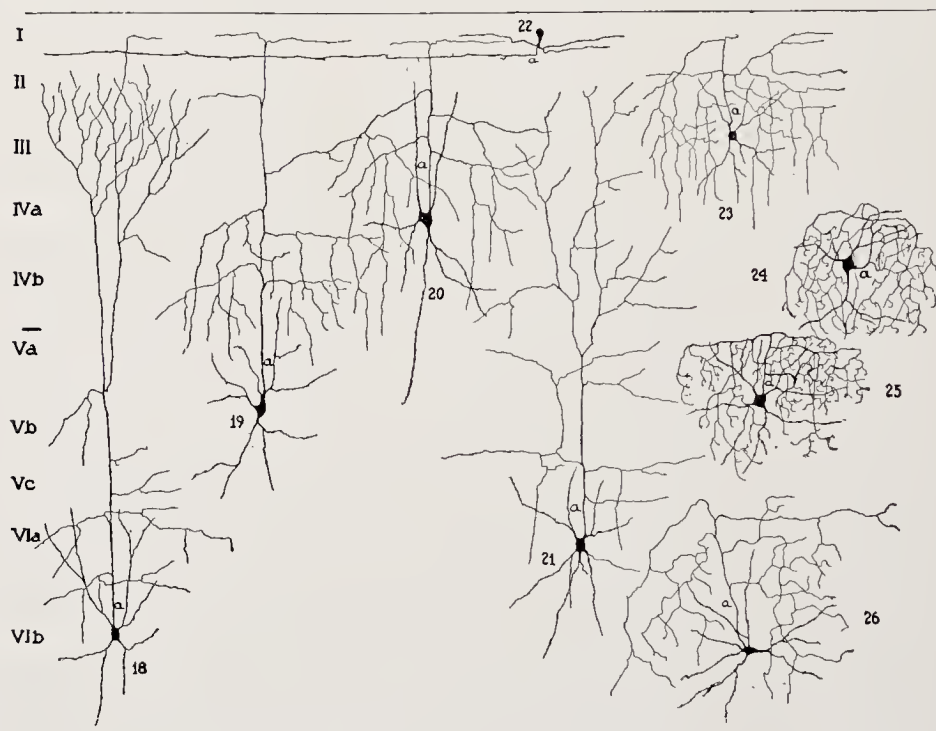


FIG. 73. Three main types of cells with intracortical axons: 18, 19, 20, 21, cells with ascending axons; 22, cells with horizontal axon; 23, 24, 25, 26, cells with short axons.

which, theoretically, the whole process of the transmission of impulses from the afferent fibre to the efferent axon may be accomplished. Within the elementary unit there are cells which establish synaptic connections with the afferent fibre and cells which make no such connections; the latter cells, of course, will be stimulated only as a result of cortical activity. Save for layers I and II, all cortical layers contain cells having synaptic contacts with the specific afferents, so that it would be improper to call any one layer "receptor." On the other hand, every layer except I has axons reaching the white matter, and therefore no layer may be called the "effector." It is true that in some cortical fields, such as the motor cortex, a powerful efferent tract arises from pyramids in layer V;

but in other fields, such as the entorhinal cortex and the occipital fields, the main efferent tracts arise from the upper layers. In every case the function of the cortex consists in stimulating distant centres, and this "effect" is sometimes accomplished by "association tracts" ending in other cortical fields, and again by "projection tracts" ending in the sub-cortical centres. Moreover, layers v and vi are the source of powerful "association" tracts.

In these circumstances it is obvious that there is no basis for considering the cortex as composed of several layers with specific primordial functions: reception, association and projection. From the functional point of view it is a unitary system composed of vertical chains of neurons, among which anatomically the most important are those starting at the articulation of the specific afferents and the cells of the external lamina. The neurons with descending axons of this lamina send their impulses to layers v and vi, from which impulses are sent back chiefly to layers ii and iii. The association fibres have their endings in layers ii, iii and vi, which are strategic places where the impulses that they conduct may modify the circulation of impulses through the cortical chains. The architectonic layers contain the bodies, *i.e.*, only a small part of the dendritic apparatus of these cells, which form similar links in the vertical chains. This arrangement must be related to the existence of cells with short axons, such as cells 24 and 25 (fig. 73). The synaptic terminals of these axons are located on the bodies of the cells with descending axons, so that when the short axon cell discharges, powerful stimuli are delivered simultaneously to a large number of neurons. Hence the assumption lies at hand that the impulses circulating through the vertical chains are synchronized at the level of the architectonic layers and sublayers. The abundance of cells with short axons and their systematic distribution suggest that at certain phases of cortical activity the cells of the various layers fire off in more or less synchronous volleys of impulses.

Since for physiology the important data are those referring to the arrangement of the neurons in synaptic chains, through which nerve impulses may be transmitted, it is of interest to consider in some detail the neuron chains present in the cortex. Some of these chains, including a large pyramid (origin of projection fibre), have been represented in the diagram of figure 74, 8; similar chains, however, may be drawn for any other type of cell. The diagram needs little explanation. The assump-

tion is that impulses enter the cortex through the specific afferents *a* and *a'*, and the synapses marked by an arrow are crossed by the impulses. It is at present believed that many of the impulses arriving at the synapses of a cell fail to cross the synapse because they do not reach threshold; but there is no evidence to prevent the assumption that any synapse is passable, provided that the conditions necessary for summation are fulfilled. For the sake of illustration, arrows have been placed on those synapses in which the convergence of the fibres of homogeneous origin favours transmission, but arrows might have been placed on any of the others. At any rate, the fact must be borne in mind that since synaptic stimulation demands simultaneous activation of several synapses, the transmission of impulses through the cortex requires the activity of many more cells than can be included in a diagram.

When, following the arrows, the successive synapses are crossed, it will be seen that impulses are delivered again and again to the same cells (fig. 74, 8), the letters *s*₁, *s*₂, etc., indicating the order of the corresponding synapse. The impulses carried by fibres *a* and *a'* arrive at synapses of the first order, those of cell 5 at synapses of the second order, those of cell 5' at synapses of the third order, those of cell 5'' at synapses of the fourth order, etc.* Since the passage over a synapse means a delay of the impulse by roughly 0.6 msec. (ch. iv), the order of the synapse indicates the time at which the impulses arrive at cells 8 after the first impulse has entered through fibres *a*. It is evident that each *a* impulse causes the cortical cells to be bombarded by a succession of impulses, thus creating in them a constant state of *facilitation*, and eventually stimulating them to discharge into their axons (ch. iv).

Two important features of the neuron chains must be emphasized: (i) All the chains, including one or several synapses, are superimposed upon the simplest chain, including only the articulation of fibre *a* and cell 8 (two-neuron arc) shown at the extreme left; (ii) The chains include closed loops, as for example, 8-2, 18-8, or 8'-2', 25-8' (fig. 74). These two

* The fact that cells of the same anatomical type, for example neuron 5, figures 71, 72 and 73, may deliver to effector neurons (fig. 74) impulses of the second, third, etc., order indicates that during cortical activity the composition of chains of neurons must certainly vary. Impulses entering cortex find many paths through which they might circulate. Some paths are passable, because conditions for summation, such as instantaneous convergence of impulses, are given. Other paths are impassable, but may become passable later when cortical activity creates impulses capable of summing with afferent impulses. At the same time some ordinarily open paths will be closed, when cortical activity raises threshold of strategic links in chains of neurons.

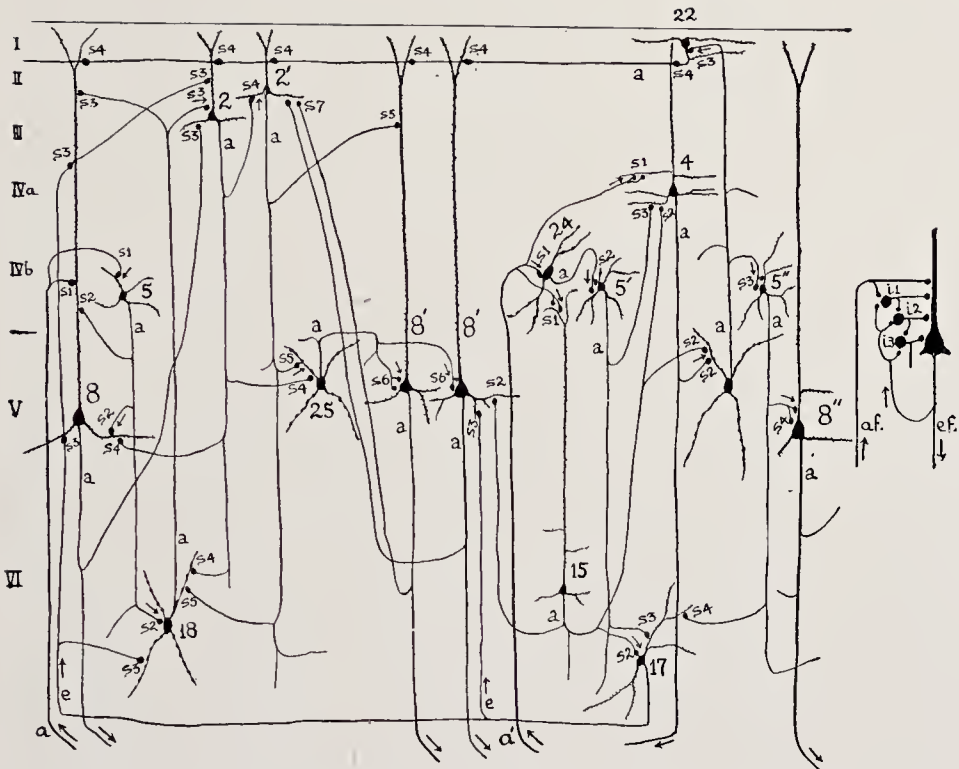


FIG. 74. Diagram of some of intracortical chains of neurons. The number on cells and letters *a* and *e* on fibres the same as in figs. 71, 72 and 73. Axons of cortical cells are marked with *a*. Note that only a few dendrites and axonal branches have been included in diagram. Synaptic junctions are indicated by letter *s* (*s*1, *s*2, etc.) and by thickening of axon. It is assumed that synapses marked with an arrow are traversed by impulses.

Small diagram at right is a simplification of diagram at left. Afferent fibre *af.* activates large pyramid which is the origin of efferent fibre *ef.* and also a system of cortical internuncial cells (*i*1, *i*2, *i*3); recurrent collateral of *ef.* delivers impulses again to internuncial system. This diagram exemplifies the broad plan upon which the central nervous system is organized.

features are graphically illustrated in the simplified diagram at the right of figure 74, which indicates that the cortical chains are in no way different from the chains of internuncial neurons in any part of the central nervous system. Fibre *a* carries the afferent impulses, cells 8, 8' and 8'' are the effector neurons; all the other neurons are internuncials. With this definition in mind, the analysis of the transmission of the impulses through subcortical centres may be directly applied to the cortex. A discussion of this problem will be found in other publications (Lorente de Nó, 1922, 1934).

When the chains of neurons in figure 74 are examined closely it will

be observed that they are of two types. Some of the chains include short links with cells of a single layer, as for example links 25-8' in layer v, and links 24-5' in layer iv. Other links are long and include cells of different layers, as, for instance, links 18-2, 15-4, 8'-2', etc. The long links vary but little in different mammals, but the short links increase progressively in number from the mouse to man. Thus, in the cortex of the mouse, cells with ascending axons are relatively numerous, while those with short axons are relatively rare. In the human cortex there is an increase in the number of cells with ascending axons, but the increase in the cells having short axons is much more pronounced, so much so that in some cortical regions they outnumber the cells with descending axons. Furthermore, the increase in the short axon cells is not restricted to any one layer, but takes place in all of them, although in different cortical regions the increase is more pronounced in certain layers, for example, in the area striata in layer iv and the motor area in layer v. *Cajal assumed that the large number of cells with short axons was the anatomical expression of the delicacy of function of the brain of man.* At present that assumption is almost a statement of fact, for it is known that synaptic transmission demands the summation of impulses under strict conditions, and it is evident that the more heterogeneous is the origin of the synapses on the cells with descending axons, the more rigid become the conditions for threshold stimulation, and the more accurate the selection of the paths through which the impulses may be conducted.* The reduc-

* Elaboration of the elementary pattern takes place not only by increase in number of cells with short axons, but also by fractionation of dendritic and axonal plexuses. For example, in the mouse fractionation of the plexus of layers ii and iii is poor, but in higher mammals, especially in man, an exquisite fractionation takes place in some cortical areas or, better said, at some places of each cortical area. The shafts of pyramids of iii do not give off side branches in ii, and even within layer iii two, three or even more sublayers appear, because the shafts of some pyramids in the main have side branches only near the cell body, and because next to the pyramids of average size small pyramidal cells appear with dendrites only within one substratum. Side branches of the vertical fibres also become grouped in substrata (cf. footnote, p. 289). The result is fractionation of the plexuses into small strata containing synapses of but few types. It is remarkable that within each architectonic field characterized by receiving one set of specific afferents, e.g., the optic radiation, there are many zones of widely different structure recognizable in ordinary Nissl pictures by their position in relation to the sulci, even to the smallest indentations of surface. Thus it comes about that area striata is composed of an enormous number of vertical parallelopipedons with the longer horizontal axis parallel to the main system of fibres in the stria of Gennari and related to the numerous shallow sulci detectable in the surface of the calcarine cortex. In each parallelopipedon, which has microscopic size, the thickness of layers and even the relative number of cells of each type varies between considerable limits. The drawing of Campbell (fig. 70) happens to include different parts of two adjacent parallelopipedons.

tion of the number of cells with short axons, without essential modification of the long links in the chains of cortical neurons, makes the cortex of the mouse the "skeleton" for the human cortex, and no objection can be raised against the use of the diagrams given in figures 71, 72, 73 and 74 as a first approximation for interpretation of experimental results obtained in the higher mammals. These diagrams reproduce the elementary cortical pattern.

Besides elaboration by the addition of cells with short axons in various mammalian brains, the elementary cortical pattern, by losing some of the cell types, for example the star cells of layer ivb or some of the long chains, undergoes simplification within the brain of each animal type. The elementary pattern in figures 71, 72 and 73, with unessential modifications, is found to be valid for the cortex of the following regions: postcentralis, parietalis, occipitalis, and temporalis. But when studying the temporal lobe, in passing over the fissura rhinalis, it is found in the area entorhinalis (fig. 70, 6) that the afferent fibres fill the entire external lamina, so that their plexus is located immediately beneath and even within the plexiform layer. There are no cells comparable to those of layers II and III of the temporo-parieto-occipital isocortex. The layer of deep large pyramids (v) becomes very thin and seems to have lost its sublayers va and vc. The structure of the entorhinal area is illustrated in figure 75 in which, it will be observed, all the pyramids of the external lamina have the same relations to the afferent fibres as the star pyramids have in the isocortex. From certain points of view, it would be permissible to compare the whole external lamina of the entorhinal cortex to layer IV of the isocortex, but the comparison would have small value and would mask the fact that in the area entorhinalis the impulses conducted by the recurrent fibres of the internal lamina meet the afferent impulses on the same cells of the external lamina, while in the isocortex the afferent and the recurrent cortical impulses are in part delivered to different cells (layers IV and II-III).

Since the cortical chains in the isocortex differ from those of the allocortex, no common pattern is valid for both, unless an important simplification is made and the temporo-parieto-occipital pattern is considered to be an elaboration of the entorhinal pattern. Then, viewing the external and internal laminae as more or less unitary systems, it may be said that the whole cortex, from the central sulcus, over the Sylvian sulcus to the occipital pole and back to the retrosplenial and callosomarginal sulci, is composed of two laminae. The upper lamina receives the specific afferents; the lower does not. The upper lamina has cells with efferent axons which reach only, or at least almost exclusively, other cortical regions (association fibres); while the lower lamina in addition has fibres of projection. Both laminae are interrelated by numerous vertical chains. In the isocortex the chains have greater complication because the number of links in each chain is larger.

No other cortical area has a simpler structure than that of the entorhinal region, because the primary olfactory cortex (Ramón y Cajal, 1900-06, and O'Leary, 1937) is in fact a subcortical centre comparable to the geniculate bodies, etc. The diagrams of figures 71 and 75 cannot as yet be said to be directly valid for the entire cortex, for the elementary pattern of the regio precentralis, frontalis, limbica, retrosplenialis, prefrontalis, and insularis is unknown. Considerable information is available about the precentral cortex, but it is in part conflicting and decidedly incomplete. Cajal's data about the insular region are fragmentary, and the findings

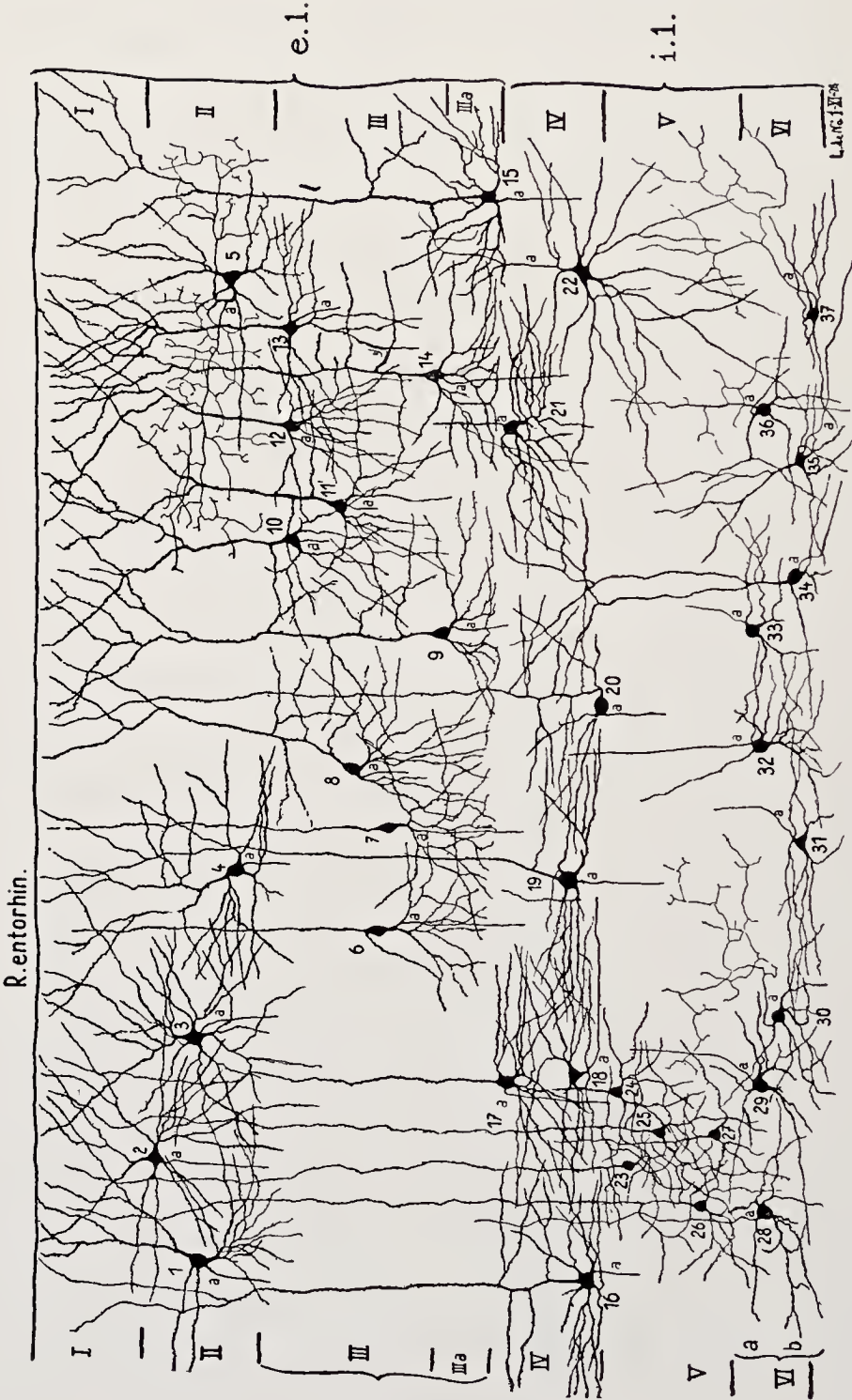


Fig. 75. For legend see bottom of opposite page.

of the present author on that and the other unknown regions are still insufficient for definite statement. Hypothetical plans of stratification of these regions have been suggested by the cytoarchitectonic schools.

How the problem of the *motor* cortex stands at the present time may be stated in a few paragraphs. In 1900 Cajal made the remarkable observation that in the human precentral cortex, although the cell layers may be compared with those of the postcentral cortex, the specific afferents end in different layers; but this fundamental observation was unfortunately made by him too late. Having first discovered the afferent plexus in the precentral cortex, he examined the structure of the postcentral cortex with the idea that the said plexus should be found in the same place as in the precentral convolution. Much to his surprise this proved not to be true. However, Cajal did not fully realize that the suggested comparison of the cell layers and dendritic plexuses in the precentral and the postcentral cortices could not be maintained. The situation was the more puzzling since Cajal found that both regions have a layer of "granules"; but while in the precentral cortex the granules are found *below* the plexus of the afferent fibres, in the postcentral cortex they are *within* the plexus of the afferent fibres. Cajal's description of the afferent plexuses is so categorical that it must be taken as a statement of fact devoid of theoretical interpretation.

The present author has not been able to study the human precentral area as completely as is necessary for a definitive solution of the problem, but fragmentary observations added to more complete studies on the motor cortex of the cat, rat, and mouse suggest that the architectonic layers of granules in the precentral area are not comparable to the granular cells of the postcentral region. The superficial stratum of granular cells of Cajal (1900, his fig. 17A) which is mixed with medium sized pyramids is perhaps comparable to the fourth layer of the parietal isocortex. But the deep layer of granules of the motor cortex can be compared only

FIG. 75. Diagram of dendritic plexus in entorhinal area (from Lorente de Nó, 1934). The numbers of layers in this area do not correspond with numbers of layers in isocortex (fig. 71). The architectonic picture of human entorhinal area is reproduced in figure 70, 6; *e.l.* and *i.l.*, the two main laminae. 1 to 4, pyramids of layer II; 6 to 15, pyramids of layer III. Note distribution of basilar dendrites and of collaterals of ascending shafts within external lamina. In IIIa there is dense plexus with but few cell bodies. 16, 17 and 19, 20, large deep pyramids with side branches only within the layer; 23 to 27, long spindles; 34, medium spindle; 35, deep star cell; 5, cell with short horizontal axon in layer II; 18, 21, 22, 28, 29, 31, 32, 33, 36, cells with ascending axons; 30, 37, cells with short axons of layers V-VI. Axons have been marked with a. In this area specific afferent fibres are distributed in layers II, III, and IIIa and lower part of layer I.

to layer va of the parietal isocortex. Hence the division of the motor cortex into two lamina suggested in figure 69, 1(*e.l.* and *i.l.*). Emphasis, however, must be placed upon the fact that the appearance of "granules" and of numerous short pyramids in the upper zone of layer v marks the beginning of a new structural pattern characteristic of the frontal isocortex.

In the case of the mouse, where the cells with short axons are not so numerous as in the cat or man, it may be found that the division of the cortex into two laminae is still possible, but also that the enormous widening of layer v, the appearance of large numbers of short pyramids in va, and the great increase in the number of deep star cells in layer v cause the appearance of vertical chains subordinated to the unspecific afferents(fig. 71, *c, d*) and association fibres(fig. 71, *e, f*) which are not present or poorly developed in the parieto-temporo-occipital isocortex.

When the changes in structure of the cortex in the regions medial to the motor cortex are studied, it is seen that while advancing toward the limbic region, layers II and III of the outer lamina become progressively thinner and the afferent plexus approaches the plexiform layer. Finally in the so-called granular limbic and granular retrosplenial regions, as originally demonstrated by Cajal, the afferent plexus lies immediately below that layer. The outer cortical lamina is, therefore, greatly reduced, while the inner cortical lamina suffers a relatively smaller reduction. This suggests that the limbic and retrosplenial structural patterns in relation to the precentral pattern are in the same situation as is the entorhinal pattern compared to the postcentral pattern.

No attempt will be made here to suggest a diagram of stratification of the frontal isocortex, for in this account all anatomical hypotheses have been avoided. Since no information on certain fundamental points is available, any stratification made would be based only on assumptions. The elementary pattern of the frontal cortex is unknown and this lack of knowledge must be frankly admitted. The architectonic schools have assumed that the so-called "granular" frontal cortex is comparable in its stratification to the postcentral cortex. This comparison of the layers of "granules" may be correct, but it also may be erroneous. Until the afferent fibres of these fields are studied in suitable material, the question can not be definitely settled.

ARCHITECTONIC CHARTS

If use is made of the concept of the elementary unit introduced previously, it may be said that the cortex is composed of an enormous number of elementary units, not simply juxtaposed but also overlapping. Each elementary unit has a series of axonal and dendritic plexuses, where the synapses between intracortical elements and afferent fibres with cortical cells are established. The bodies of the cells which form similar links in the intracortical chains are grouped in horizontal layers. Therefore any change in the constitution of the intracortical chains must produce a variation also in the density of the plexuses, *i.e.*, in the Nissl pattern, in the size of the empty intercellular spaces, and likewise in the number of cells in each layer. As the Nissl method stains only the cells, but leaves the plexuses unstained, it does not yield absolute data regarding the structure of the cortex. It does, however, reveal its relative changes. The detection of structural modifications is made easier by the fact, forcibly demonstrated by O. and C. Vogt (1919) and later by M. Vogt (1933), that the changes take place simultaneously in several layers and often in all the layers. This was indeed to be expected, for the cortical neurons are arranged in chains that include cells from several layers, and a change in one layer must bring about changes in the others. The Vogts also have demonstrated that the changes take place not through transition zones, as assumed by Brodmann (1909) and later by von Economo and Koskinas (1925), but suddenly.

The ability of architectonics to detect changes in structure on the basis of the cytoarchitectonic Nissl picture or of the Weigert myeloarchitectonic stain cannot be questioned, not only because these studies have a sound theoretical foundation, but also because when they are complemented by selective methods, such as the Golgi or Golgi-Cox, the architectonic changes are found to be sharp and accompanied by alterations of the plexuses (Lorente de Nó, 1934a, p. 433). A difficulty arises when it is desired to set a limit to the parcelling. Campbell described 20 different fields in the human brain, Elliot Smith increased the number to 50, Brodmann also mentioned about 50, but in 1919 the Vogts announced the existence of over 200 fields. And even this number seems now to be too small, because the careful parcellations of some areas of the human brain and that of primates made by Rose (1935) and E. Beck (1928) have revealed that the cytoarchitectonic divisions may be carried much farther than was previously thought desirable. A study of the excellent photographs published by the Vogts, Rose and Beck leaves no doubt that the architectonic differences really exist, and also that the divisions can be carried even farther. The recent parcellations made by E. Beck (1929a) of the areas of the occipital lobe afford conclusive proof in this respect.

Architectonics is, therefore, an analytical tool which if used intensively will lead to an elaborate parcellation of the brain; theoretically, it should be possible

by its use to go down almost to the elementary unit. However, the number of architectonic fields cannot be definitely stated, as it depends on the degree of change in the architectonic picture which the observer selects as standard. It is no secret that the classical architectonic charts were not made with uniform standards. Many architectonic fields were differentiated at the level of the central sulcus, because that region was intensively studied; later a comparable number of fields in the temporal lobe was described by Vogt and Beck and in the occipital lobe by Beck. In striking contrast to these parts of the architectonic charts, the parietal lobe is described as having only a few fields, but no author has published a parcellation made on the basis of a rigorous criterion.

It is an immediate consequence of the histological methods used in architectonic research that the nature of the changes at the boundary of fields remains unknown. For that reason any architectonic criterion which aims to divide the field boundaries into categories and to group the fields into larger divisions must be faulty. Only one example need be mentioned. In Ammon's horn, an area most suitable for architectonic studies, limits as important as those due to the ending of certain afferent tracts were ignored by the cytoarchitectonic school, and instead there were suggested limits for which no significant change in intercellular connections could be detected. In these circumstances there can be no doubt that architectonics requires the help of other lines of research, anatomical and physiological, to group the individual fields into larger regions. The present grouping into regions, which is in fact made according to the macroscopic anatomy of the human brain, is clearly untenable. It is related to the projection of the thalamus into the cortex, but only along general lines. There can be no question that some of the areas, for instance the frontal region, contain heterogeneous fields offering differences more marked than those existing between, for example, the granular and the agranular limbic regions.

The recent development of cytoarchitectonics for which the Vogts, Rose and E. Beck are to be credited has demonstrated forcibly the shortcomings of the classic comparative cytoarchitectonics. Brodmann published charts of a number of different mammalian brains which it was believed were comparable. The individual fields were numerated in the same manner in the various mammals, and it was indicated that fields with the same numbers were homologous; it was further assumed that some fields were phylogenetically young, and specific human fields were described. Brodmann's concept has proved to be erroneous. It is not difficult for experts in cytoarchitectonic research to ascertain the way in which Brodmann established the "homology" between the fields of different mammals. Parcellations of the individual brains were made and a few fields were homologized on the basis of reliable data. These fields included the areas gigantopyramidalis, limbica, retrosplenialis, insularis, striata, and perhaps one or two more. The other fields were numbered hypothetically, not on the basis of specific structure, but on their gross anatomical relations to the known fields. This procedure, it must be stated, was not entirely unjustified, but it demanded parcellation of the individual brains with comparable criteria. In some of the larger brains, Brodmann differentiated many more fields than in the smaller brains for which he used a less rigorous architectonic criterion, and therefore a phylogenetic increase was assumed. However, when later Beck (1928) parcellated the temporal lobe of the chimpanzee, he found that it contained many more fields than had previously been suspected, that it had in fact the same main fields as has the temporal lobe of man. Parcellation of the occipital lobe of the macaque (Beck, 1934) also revealed the existence of numerous subdivisions heretofore unsuspected.

It may be found that some of the new field boundaries used are artificial and irrelevant, but anatomically they are of the same order as the boundaries in the central convolutions, for the value of which experimental physiology has afforded conclusive proof. What the division of the brain into fields means is not a problem of architectonics, but rather one of experimental physiology and clinical neurology. Physiological research will no doubt group the small fields into larger units, but it must also analyze the role played by even the smallest anatomical subdivision. How many fields the individual mammals have is unknown. There is no doubt but that all mammals must have nearly the same major divisions of the cortex, because the thalamic nuclei do not differ in a radical manner from mammal to mammal; as a matter of fact, however, nothing is known about the smaller subdivisions. The evolution of the structure of the cortex in the mammalian series reveals itself chiefly in an increase in the relative number of cells with short axons without essential alteration of the elementary pattern. Possibly future research will lead to the establishment of an elementary "field pattern," including the thalamic nuclei, and then it may be hoped that the comparative anatomy of the brain will be successfully studied. For one set of fields, those of the Ammonic system, an elementary pattern has already been established and it is found that this remains constant for every mammal, from the mouse to man; but whether conclusions drawn from the study of a system may properly be applied to the rest of the cortex is an open question.

A complete chart of the human brain or of the brain of primates is not yet available. The published charts of Vogt, Rose and Beck include only segments of the brain. A general orientation, however, can be obtained by a study of the old charts of Campbell(1905) (fig. 76A) and the similar ones of Brodmann(1909) (fig. 76B); also of the chart of von Economo and Koskinas(1925) which, in fact, is Brodmann's chart with unsystematic elaborations.

PRINCIPAL AREAS

The principal cortical areas will be grouped in accordance with the anatomical lobes of the cerebral hemispheres, and within a given lobe only those subdivisions will be recognized which at present have physiological significance.

FRONTAL LOBE. The frontal lobe is limited by the central sulcus and the sulcus callosomarginalis: in its ventral surface it also contains parts of the olfactory allocortex. However, from the point of view of architectonics it is customary to include only the isocortical fields of the frontal lobe. In the frontal lobe there are several important areas concerned with the production of voluntary movements (motor and premotor cortices). Campbell divided the frontal lobe into precentral (or motor), intermediate precentral, frontal and prefrontal regions. A similar division was suggested by Brodmann who, however, subdivided some of Campbell's

areas. Physiological and architectonic studies of the Vogts revealed that Brodmann's subdivisions were incomplete and suggested a new subdivision (ch. XXI). A considerable amount of physiological experimentation has been carried out on the following regions.

Area 4 (Motor area). This begins within the depths of the central sulcus, generally part way up the anterior wall, and is characterized by the presence of the giant pyramidal cells of Betz in layer v. For convenience of designation the superior middle and inferior parts of this region are designated areas 4a (leg), 4b (arm) and 4c (face), respectively (Vogt, 1919). They differ from one another only in the size of the Betz cells, those of area 4a being the largest and those of area 4c the smallest. The relation of area 4 to the gross anatomical landmarks of the hemispheres varies in different primates. In man area 4 is largely concealed within the central sulcus: thus area 4b (the arm representation) scarcely emerges from the central sulcus, but area 4a (motor representation of the lower extremity) extends about one cm. rostrally on the lateral surface of the gyrus precentralis (fig. 76). In the baboons and monkeys area 4 is for the most part exposed on the lateral surface of the hemisphere. The orang and chimpanzee have a less exposed area 4 than the monkey and thus lie intermediate between the monkey and man. A comparative study of the cytoarchitecture of areas 4 and 6 in various primates has recently been made by Bucy (1935).

The anatomical boundaries of area 4 are: posteriorly the base of the central sulcus, except in the most superior part of the convexity of the hemisphere where it passes somewhat rostral to the central sulcus, and continues on to the medial surface of the hemisphere down to the sulcus cinguli. The latter sulcus forms the inferior boundary of area 4 on the medial surface. The rostral boundary of the motor area is less well defined. Laterally on the hemisphere in monkeys and chimpanzees it lies somewhat caudal to the inferior limb of the arcuate or inferior precentral sulcus; rostrally it has no external anatomical landmarks, but extends upward more or less parallel to the central sulcus, generally dividing the superior precentral sulcus near its rostral end (fig. 76). The rostral boundary then passes somewhat upward and over to the medial surface as far as the sulcus cinguli. In macaque and chimpanzee the rostral border of area 4 is irregular because the Betz cells become unevenly sparse in the region of the superior precentral sulcus (Denny-Brown, unpublished; Bucy, 1935).

"Strip" region. The area of transitional cortex between area 4 and 6 in which the Betz cells are scattered has proved to be one of functional significance in the pathogenesis of spasticity in macaques. According to Hines (1936, 1937) the strip region occupies some 3 mm. of precentral cortex at the rostral limit of area 4. It is identical cytoarchitecturally with area 4 except for the sparse distribution of Betz cells (ch. XXI). It has also been identified in chimpanzee by Dusser de Barenne and McCulloch (1941).

Area 6 (Premotor). The rostral part of the precentral convolution, generally known as the "premotor area," is histologically similar to area 4, except for the absence of the giant pyramidal cells of Betz in the fifth layer. The cells of the fifth layer are pyramidal in shape and obviously motor in type, as was originally pointed out by Campbell (1905). Large pyramidal cells of the Betz type are sometimes found sporadically in area 6, particularly in the macaque.

The boundaries of the premotor area are somewhat less definite in terms of anatomical landmarks than those of area 4. The caudal limit is the rostral boundary

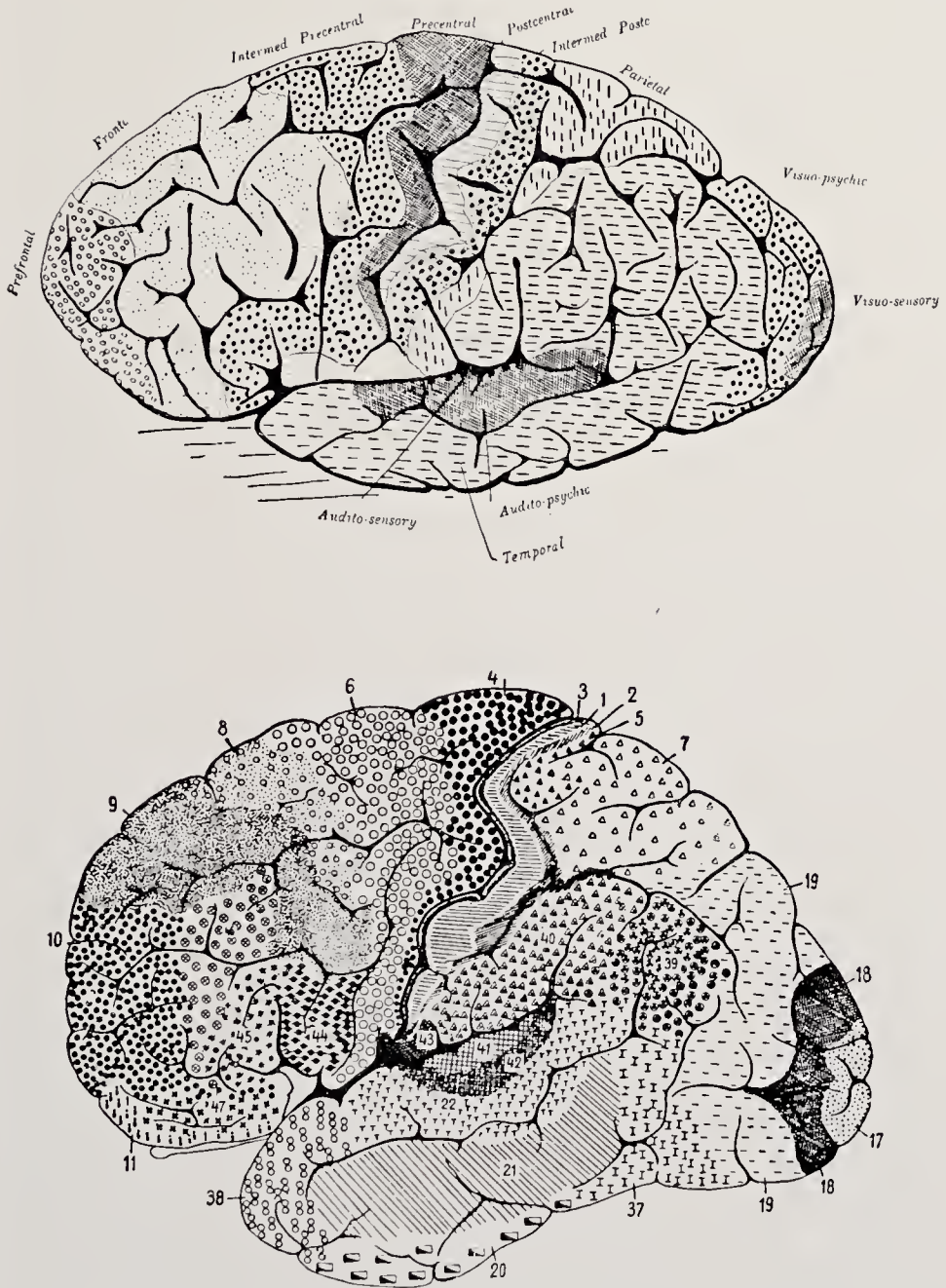


FIG. 76. Cytoarchitectural maps of human cortex. A, Campbell's map(1905), the prototype of all subsequent cytoarchitectural charts of human brain. B, Brodmann's map(1909) giving his numerical designation of principal areas.

of area 4 (see above); the inferior and rostral boundary is formed in monkeys by the superior limb of the arcuate sulcus, and the upper part of the rostral boundary is the arbitrary upward continuation of the arcuate sulcus and is without cortical marking. Area 6 extends on the medial surface of the hemisphere to the sulcus cinguli as with area 4. Its boundaries in man are indicated in figure 76. Area 6 has been divided by the Vogts (1919), Foerster (1936b) and others into a number of sub-areas based on cytoarchitecture and upon specificity of response to stimulation (fig. 99). Strictly speaking the premotor area is restricted to the superior part of area 6a; the premotor area itself is divided into two regions, area 6a β and 6a α , which are functionally discrete. Brodmann and the Vogts point out that area 6 tissue is also found lateral to the inferior end of the motor area (area 4c). This region has subdivisions as follows: areas 6a α (lower part) and 6b α and 6b β , which are primarily concerned with buccal and respiratory musculature. The subdivisions are also well developed in the chimpanzee (Walker and Green, 1938). In man area 6a α (lower part) is much elaborated into a special region concerned with speech and generally referred to as Broca's area. (See areas 44 and 45 of Brodmann's map in fig. 76b).

Area 8 (Frontal eye field, Mauss, 1911). A specialized part of the frontal lobe occupying the posterior part of the second frontal convolution (fig. 76b) is clearly motor in function and in the monkey lies just rostral to the arcuate sulcus (fig. 93). The superior part of this region is referred to by the Vogts as area 8a $\beta\delta$ and the most lateral part as area 8 γ . From the point of view of cytoarchitecture area 8 is transitional cortex (between areas 6 and 9). It has an extensive extrapyramidal projection to the striatum, thalamus (lateroventral nucleus), subthalamus and tegmentum (Hirasawa, 1935).

Areas 9, 10, 11 and 12 (Prefrontal area). The prefrontal area includes all the cortex lying rostral to areas 6 and 8 (in man to areas 6, 8 and 45) and is sometimes referred to as the "frontal association areas." From the point of view of cellular structure it is strikingly different from areas 4 and 6. The motor cells, large and small, are virtually absent from layer v. In monkeys the chief part of the region is included in Brodmann's area 9. Areas 10, 11 and 12 are all similar in structure, but their laminar peculiarities need not concern us until more is known about their functional significance. Areas 13 (respiratory area) and 14 (olfactory sulcus) have recently been delineated by Walker (1940).

PARIETAL LOBE. The parietal lobe is formed of the region of the cerebral cortex lying between the central sulcus, parieto-occipital sulcus, Sylvian fissure and the midline. As indicated in figure 76b, it includes a number of discrete regions primarily concerned with somatic sensory functions, though auditory and visual associations probably take place in the posteroinferior part of the parietal lobe (supramarginal gyrus). The more important regions are as follows (Ingalls, 1914):

Areas 3-1-2 (Postcentral area). This region which occupies the postcentral convolution receives enormous projections from the posteroventral nucleus of the thalamus, and it forms a characteristic example of sensory cortex. In the depths of the central fissure area 3 joins area 4, generally in the anterior wall. The laminae are distinct with all six layers well defined (fig. 69).

Area 5a (Preparietal area). This again is very typical sensory cortex with all six

layers well developed. Area 5 differs from 3-1-2 in having large deep pyramidal cells, some as great in size as the smaller Betz in area 4. These large motor cells were first described by Cajal and are present in monkeys as well as man. Levin (1938) has recently shown that they undergo retrograde degeneration in the macaque with lesions of the spinal cord. They evidently, therefore, contribute to the corticopontine (Sunderland, 1940) and corticospinal projections (see Peele, 1942).

Area 5b (Superior parietal area). This forms the superior part of the parietal area and occupies a large surface both in man and ape, extending down the medial surface of the hemisphere to include the precuneus (fig. 76B). There are no large pyramidal cells in the fifth layer of this area.

Area 7 (Inferior parietal area). Area 7 constitutes most of the inferior parietal lobe. Its cytoarchitectural structure closely resembles that of area 5b. The line of demarcation between 7 and 5b is difficult to establish and has not yet been determined satisfactorily in the macaque monkey or chimpanzee. Area 7 includes the "supramarginal" and "angular" gyri which are sometimes separately designated as areas 40 and 39 respectively (fig. 76B). The supramarginal and angular gyri do not materially differ in structure from the other parts of area 7. Campbell (fig. 76A) considered as temporal a part of the zone later called parietal by Brodmann, but both called area 7 parietal.

TEMPORAL LOBE. The temporal lobe, which is bounded by the parietal lobe, the Sylvian fissure and the occipital lobe, forms a large part of the total mass of the cerebral cortex. From the point of view of physiological analysis the most important regions are the temporal transverse convolutions of Heschl, where the acoustic radiation from the internal geniculate body has its terminal station. The area called auditosensory by Campbell, and area 41-42 of Brodmann, may properly be designated the "primary acoustic cortex." Numerous other areas have been differentiated in the human temporal lobe by Vogt and by Beck, it being remarkable that Beck (1928) has been able to find in the temporal lobe of the chimpanzee the same major areas as in the human temporal lobe. Apparently there are no specific human temporal fields (see Rundles and Papez, 1938).

OCCIPITAL LOBE. The occipital lobe which is wholly concerned with vision is made up of at least three regions: area 17, the striate cortex; area 18, the occipital area; and area 19, the preoccipital region. Campbell divided the occipital lobe into visuosensory and neuropsychic areas, which respectively correspond to Brodmann's area 17 and areas 18 and 19. The area striata (17) receives the optic radiation from the external geniculate body. It may be properly called the primary visual cortex. Recent work of Minkowski, Polyak, Brouwer and others has demonstrated that it receives an anatomical projection of the geniculate body in the area striata (ch. XVII). It also sends motor projections. The rest of

the occipital lobe, according to recent studies by Beck, contains a much larger number of fields than previously suspected; the old division in areas 18 and 19 is therefore insufficient.

Area 17 (Striate cortex). The area striata has a well known and very characteristic cyto- and myeloarchitectonic structure. Layer IV is duplicated in two separate strata; the line of division of this layer into two separate laminae marks the boundary of area 18, the parastriate or occipital cortex. The space between these two duplicated layers is occupied by a band of white myelinated fibres which gives rise to the line of Gennari; this is visible to the naked eye and was the first evidence to be discovered of architectural organization in the cortex (see historical note above). The fibres in this stria are made up of the projections to and from the lateral geniculate bodies plus an enormous number of intracortical association fibres (for details see O'Leary, 1941).

Area 18 (Occipital area). This large area occupies the lateral, and also medial, surface of the occipital lobe, extending from the midline laterally and inferiorly around area 17. In the fourth layer the line of Gennari, though present, is not detectable by the naked eye.

Area 19 (Preoccipital area). Strictly speaking, area 19 lies within the posterior parietal lobe. Its cytoarchitectural characteristics are similar to those of area 7, but its connections appear to be primarily with the pulvinar.

ALLOCORTEX

The allocortical fields have not been widely studied experimentally. From studies of comparative anatomy it has been concluded that the allocortex (the rhinencephalon of Kölliker) is a part of the olfactory and allied systems, and it is assumed that the sensory areas, where cortical representation of smell and taste begins, are located in the retrosplenial (29 of Brodmann) and entorhinal (28 of Brodmann) regions; however, despite the known facts relative to the allocortical efferent system, especially those of Ammon's horn, the origin of the afferent tracts is still a baffling problem (O'Leary, 1937).

MOTOR PROJECTIONS FROM ISOCORTEX

During the past few years many important advances in knowledge of the motor pathways from the cerebral cortex have been made both in men and related primates. The most important disclosure — though not wholly new except in emphasis — is the recognition of a vast extrapyramidal projection arising in many parts of the cerebral cortex. The cortical projections fall naturally into two groups: (i) the pyramidal pathways arising from areas 4 and 5, and to some extent also from other areas of the pre- and postcentral convolutions, and (ii) the extrapyramidal systems arising from all parts of the frontal lobe and also from areas 3-1-2,

5, 7 and 22 of the parietal and temporal lobes; there are also specific corticothalamic and corticomesencephalic projections from the occipital lobe. The principal pathways from the cortex are as follows:

PYRAMIDAL(CORTICOSPINAL)PROJECTIONS. The corticospinal projections in man and other primates springs largely from the precentral convolution. Holmes and Page May(1909)believed that the pyramidal tract took origin solely from the Betz cells in area 4. They based their conclusions upon a series of clinical and experimental studies of the cerebral cortex after lesions of the spinal cord; on analyzing the retrograde degenerations in the frontal lobe obvious chromatolytic changes were found in the Betz cells. More recently it has been established that the giant pyramidal cells originating in areas 2 and 5b of the parietal lobe also undergo retrograde changes after spinal lesions, and it is clear that they likewise contribute to the corticospinal system (Peele, 1942). Following spinal lesions Schroeder(1914), Minkowski(1923)and von Economo and Koskinas(1925)believed that they had found evidence of retrograde cell changes in the larger pyramidal cells of layer v in area 6. Levin(1936c), however, is doubtful of these changes and believes that when present they are restricted to heterotopic Betz cells in area 6. Marchi degeneration reported(Kennard, 1935b)from lesions of area 6 was attributed by Levin to such heterotopic Betz cells. The matter, however, is not closed and further studies of the pyramidal cells in area 6 following spinal injuries are needed; the more so because Campbell(1905, p. 34)estimated the total number of Betz cells in each hemisphere of man as 25,000, while the total number of fibres in each pyramidal tract is said to be ten times as great.

In a series of six important papers on the human pyramidal tract Lassek(1938-42)finds that there are approximately 1,000,000 fibres in a single human pyramid, of which 688,800 or 61 per cent were myelinated, and that of the myelinated fibres those of large diameters form a relatively small proportion of the total number, the ratios being as follows: 11-22 μ 1.73 per cent, 5-10 μ 8.7 per cent, 1-4 μ 89.57 per cent. In the human motor area, by contrast, there were in one instance only 34,183 Betz cells, of which 75.5 per cent were in the upper, 17.9 per cent in the middle, and 6.6 per cent in the lower third of area 4. The numbers of Betz cells were approximately the same on right and left. The Betz cells thus contribute two to three per cent of fibres in the pyramidal tract. Betz cells in man vary in size between 900 and 4,100 sq. microns, those in the upper third being considerably larger than those in the middle or lower thirds. At birth Lassek finds that no large fibres are visible in the pyramids. At eight months large fibres begin to appear, but they do not reach their full growth until well after adolescence(*ca.* 22 years). At 80 years the fibres of the pyramids, on the basis of one case, showed a decrease both in their size and number.

Lassek has also made a comparative study of the pyramids of various mammals, including the monkey. The macaque pyramid contains 554,000 fibres with an average of 18,845 Betz cells and a somewhat similar distribution of Betz cells in area 4 and of small fibre diameters in the pyramids. Lassek concludes from his work on man and animals that the pyramids take origin, not only from area 4 but from smaller motor cells elsewhere. Talmage Peele(1942) reports that areas 3-1-2, 5 and 7 of the parietal lobe all give rise to corticospinal fibres, but principally those of small diameter. He believes that these fibres terminate upon interneurons of the dorsal horn, in this way deflecting incoming sensory influences to higher levels of integration(long-circuiting).

The course of the corticospinal tract through the anterior two-thirds of the posterior limb of the internal capsule, the middle part of the cerebral peduncle, and the pons into the pyramids of the medulla to their decussation is too well known to require a full description. It should be mentioned, however, that throughout their course the pyramidal tracts maintain a highly discrete spatial organization; thus in passing through the internal capsule the fibres from the leg area remain segregated in the posterior end of its posterior limb, and in the cerebral peduncle and pons they are laterally disposed, while those from arm and face are more medially placed. Similar lamination occurs in the lateral pyramidal tract in the spinal cord.

It is sometimes forgotten that on reaching the spinal cord the pyramidal tracts divide into three discrete bundles, two of them made up of uncrossed fibres, the third and larger division of contralateral fibres. They are as follows:(i)an *uncrossed ventral tract*, present in man and chimpanzee, and generally referred to as the tract of Türeck(1851): these fibres originate in the posterior part of area 4, but often they do not descend to the lower levels of the cord;(ii)an *uncrossed lateral tract* passing in the lateral column of all primates thus far examined, and in the chimpanzee constituting at least one-tenth of the corticospinal projection (Fulton and Sheehan, 1935);(iii)a *crossed lateral tract* common in all mammals: it passes to the lower segments of the spinal cord only in the higher mammalian forms. The crossed tract generally constitutes 70-85 per cent of the corticospinal projection of chimpanzee and man. Leyton and Sherrington(1917, p. 185), who also observed both categories of uncrossed pyramidal tracts in the chimpanzee, were convinced that the majority of the ipsilateral corticospinal fibres actually terminated in the ventral horn of the same side rather than crossing to the opposite side of the cord in the lower spinal segments.

SITE OF TERMINATION OF PYRAMIDAL FIBRES. E. C. Hoff has elaborated

Cajal's technique of staining the synaptic terminals of the degenerating pyramidal and other descending fibre systems in the spinal cord (ch. iv). After a lesion of area 4 the neuron terminals in the cord, like those of a cut dorsal root, exhibit a characteristic swelling which may readily distinguish them from a normal termination (fig. 19). By this technique it has been established in the mature monkey and chimpanzee that the majority (at least 80 to 90 per cent) of all the pyramidal fibres terminate, not on anterior horn cells, but upon internuncial neurons, generally in the intermediate area; *this indicates that the corticospinal tracts end at a vantage point which allows them to control all incoming sensory impulses.*

Hoff and Hoff (1934) have found, in the second place, that between 20 and 25 per cent of the corticospinal fibres establish *ipsilateral* connections with the internuncial neurons of the spinal cord; few appear to terminate upon ipsilateral anterior horn cells. The distribution of the ipsilateral terminals varies with the cortical lesion; thus, if the motor area is removed after complete disappearance of all fibres from the strip and premotor regions the uncrossed degeneration is still present and is restricted mainly to the cells in the mid-region of the spinal grey matter. With strip and premotor lesions the proportion of ipsilateral terminals is greater and they are more diffusely scattered. The studies of E. C. Hoff have thus established for the first time the existence of a large proportion of ipsilaterally *terminating* corticospinal fibres, and his work also points to the paucity of direct connections with motor horn cells.

EXTRAPYRAMIDAL MOTOR PROJECTIONS FROM CORTEX. In addition to the corticospinal projections, the cerebral cortex in the higher forms gives rise to a vast extrapyramidal projection passing to many subcortical levels. Apart from the corticopontine tract there has been curiously little discussion of the extrapyramidal projection from the cortex in man. The corticothalamic system, although recognized early, had not been studied until recently (ch. xiv), and the corticonigral and corticorubral tracts are scarcely mentioned in neurological literature although both systems are evidently large (Beevor and Horsley, 1902). It seems desirable, therefore, to restrict discussion of the extrapyramidal projections to a known form, *e.g.*, the macaque, in which the projections are undoubtedly similar to those in man. These systems have been studied by Minkowski (1923), Polyak (1932), Mettler (1935), Levin (1936c), Uesugi (1937) and Hirasawa, *et al.* (1935, 1936). As Levin's is the most detailed study that has yet appeared of the frontal projections, the following summary is drawn largely from his work; the account of the parietal, temporal and occipital lobes is based on the studies of Polyak (1932)

and Mettler(1935), and the more recent studies of Verhaart and Kennard(1940).

Corticopontine tract. There are four major projections from the cortex to the pons both in man and monkey: frontopontine, parietopontine, occipitopontine and temporopontine(Sunderland, 1940). The frontopontine is much the largest; it arises about equally from areas 4 and 6 of the frontal lobe. The fibres which are of medium caliber pass with the corticospinal fibres through the posterior limb of the internal capsule and in the middle segment of the cerebral peduncle. They terminate for the most part in the anterior portion of the dorsal pontine nuclei, the fibres from area 4 terminating laterally and those from area 6 more medially. The prefrontopontine part of the tract passes through the anterior limb of the capsule and the innermost segment of the cerebral peduncle; this tract is generally known as Arnold's bundle. Its origin is not clearly established in man, but in the macaque it comes from the inferior frontal gyrus(areas 9 and 10), some of the fibres terminating in the substantia nigra; others in the dorsomedial pontine nuclei.

The temporopontine projections which pass in Türeck's bundle are also well established in the macaque's inferior and middle temporal gyri(Mettler, 1935). The parietal and occipital lobes may also contribute to this system(Sakuma, 1937, and Sunderland, 1940).

Corticonigral tract. Although seldom mentioned in connection with cortical projections, it is now clear from the work of Levin and Mettler that the substantia nigra receives a rich projection from the cortex principally from areas 4 and 6, from the temporal lobe and from area 5b of the parietal lobes(Mettler, 1935). Fibres pass through the stratum intermedium of the cerebral peduncle; in total bulk the tract is approximately equal to that of the frontopontine system. This places the substantia nigra as a subcortical motor nucleus under direct control of the cerebral cortex(Hirasawa and Kariya, 1936).

Corticotegmental(and bulbar)tract. This is a fairly large system and derives from areas 4, 6 and 8, principally from 8(Hirasawa and Kato, 1935). From the supramarginal and angular gyri a large projection passes to some of the eye muscle nuclei(Mettler, 1935, and Barris, 1936); a few also originate in the temporal lobe. The bulbar group fibres pass to the reticular substance, but these could not be traced to any of the cranial nerve nuclei.

Corticorubral tract. This system again rises principally from areas 4 and 6, passes through the posterior limb of the internal capsule and enters the superior radiation of the red nucleus by the way of Forel's tegmental field. This tract is not large and no fibres are contributed by the prefrontal region(Levine, 1936; Hirasawa and Kariya, 1936). The parietal lobe, however, contributes a large number of fibres principally from areas 3 and 5(Mettler, 1935, and Sakuma, 1937).

Corticomesencephalic tract. This tract is quite separate from that reaching the tegmentum by the substantia nigra; it is made up of a compact bundle of fibres, passing along the medial tip of the cerebral peduncle, medial to the subthalamic body. It arises in the prefrontal region in the same area as Arnold's bundle. According to Mettler(1935)the superior parietal region(areas 5b and 7)contribute fibres to the vth, viith and ixth nerve nuclei.

Corticostubthalamic tract. This is a relatively unimportant tract found arising principally from areas 4 and 6 of the frontal lobe, which passes into the subthalamic area. No degeneration could be traced into the body of Luys.

Corticothalamic system(see above p. 271). This system of fibres which un-

doubtedly arises from the many areas of the cortex has its particular focus in area 9 of the prefrontal region. It has been fully described in chapter xiv.

Corticostriate system. In Levin's experience prefrontal lesions caused degeneration in the subcallosal layer over the head of the caudate nucleus. Postcentral lesions cause similar changes more posteriorly. No degenerated fibres were seen in the caudate nucleus itself. This nucleus contains very few myelinated fibres. In one experiment in which all frontal lobes had been removed, Levin also saw bundles of degenerated fibres passing to the globus pallidus. He believes that these fibres come from the prefrontal region. Hirasawa and coworkers (1935, 1936) describe an extensive corticostriate connection from areas 8 and 9 to the head of the caudate, putamen and globus pallidus (Levin, 1936c); following a small lesion of area 8 they also found a few fibres entering the globus pallidus. Cajal (1911) describes corticostriatal connections; a number of cortical projection fibres while passing through the striatum leave collaterals in it. Lorente de Nó has confirmed the fact many times. It is, however, unknown whether all or only some areas have striated connections. More recently Verhaart and Kennard (1940) have failed in Marchi section to trace corticostriatal fibres in macaques.

Corticohypothalamic tract. The only description of a direct corticohypothalamic tract is that of Mettler who maintains that the anterior part of the marginal gyrus (area 7) contributes a direct system of fibres to the hypothalamus; he states that often fibres come also from the frontal lobes. According to Cajal (1911) corticohypothalamic connections are very numerous, but it seems that they have their origin chiefly in the allocortex and allied zones.

Occipital projections. From the occipital lobes, motor projections pass both to the geniculate bodies and to the colliculi. The exact site of termination of many of these fibres is not yet established (cf. Polyak, 1932, also Koikegami and Imogawa, 1936).

It is thus obvious that all important subcortical levels are in direct anatomical connection with the cerebral cortex. The hypothalamus, as already seen in chapter xiii, is influenced by the isocortex directly and through a variety of secondary channels, *i.e.*, the anterior and medial nuclei of the thalamus and to some extent by direct connections. The corticostriate connections will be discussed in greater detail in chapter xxiv.

Another fact often overlooked is that area 4 contributes extensively to the extrapyramidal projection as well as to the pyramidal tract, a point first established by Mellus (1895, 1899). Accordingly a lesion of area 4 will affect not only the corticospinal innervation but extrapyramidal as well. Levin's studies indicate, moreover, that in the macaque the extrapyramidal projection from area 4 and that from area 6 are virtually indistinguishable on the basis of their distribution and destination, *i.e.*, they each contribute about equally to the pontine, nigral, tegmental and rubral projections, but the individual projections no doubt have a definite organization.

SUMMARY

Modern research on the cortex has proceeded along two different lines: the study of the intimate structure of the cortex and of intracortical connections, and the subdivision of the brain into regions of specific architecture. Architectonic studies made on the basis of stains of the bodies of the cells (cytoarchitectonics) or of stains of myelinated fibres (myeloarchitectonics) have revealed that the human brain contains several hundred areas, differently built, which may be grouped into a few regions corresponding roughly to the lobes and other major divisions of the old anatomists. A first division in allocortex and isocortex is made on the basis of the existence of a superficial layer of myelinated fibres, which layer is white in the fresh brain; it is considerably more prominent in the allocortex. This division corresponds roughly to that in the rhinencephalon and the pallium of old anatomists. The main regions of the isocortex are prefrontalis, frontalis, intermediate precentralis, precentralis, postcentralis, parietalis, occipitalis, temporalis and insularis, and those of the allocortex are limbica, retrosplenialis, entorhinalis and Ammon's horn formation. A *complete* chart of the brain of man or of any mammal is not as yet available. Brodmann's numerical designations of the principal fields have been adopted for descriptive purposes.

Studies on the fine structure of the cortex have revealed that, although in architectonic pictures the horizontal stratification seems to be the most important factor in cortical organization, the intracortical connections are established chiefly in vertical directions so that the whole vertical section of the cortex must be considered as a unitary system. The cortical cells are arranged in vertical chains and the architectonic layers indicate only where the bodies of cells, which are similar links in the chains, are located. But those cells, by means of long dendrites, establish connections in other layers. The elementary pattern of the postcentral-parieto-temporo-occipital isocortex is described and compared with the simpler pattern of the entorhinal cortex. It is emphasized that the pattern of the precentral, frontal, retrosplenial and limbic cortices is still unknown.

The white lines separating certain of the cortical laminae are due to strata of medullated fibres. The best known is the line of Gennari, in the area striata of the occipital lobe (visible to the naked eye). The same line is present, although less thick, elsewhere in the cortex, and there is

known as the external line of Baillarger. The Gennari-Baillarger lines form the outer part of the fourth cortical lamina. The internal stria of Baillarger corresponds with the inner half of the fifth lamina (internal pyramidal layer). The line of Kaes and Bechterew is found on the outer margin of the third cortical lamina (external pyramidal layer).

The principal projections of the cerebral cortex fall into two groups: pyramidal or corticospinal, and extrapyramidal. The corticospinal pathways take origin principally from the Betz cells of the sixth cortical layer of areas 4 and 5a of Brodmann; possibly some fibres are contributed from large pyramidal cells of areas 5b and 6.

The extrapyramidal projections include: corticopontine, corticonigral, corticotegmental, corticorubral, corticomesencephalic, corticothalamic, corticostriate and miscellaneous motor projections from the parietal, temporal and occipital lobes.

XVI

CEREBRAL CORTEX: THE OLFACTORY SYSTEM

HISTORICAL NOTE

David Ferrier(1876)remarked pertinently, "The position of the olfactory center may with great probability be inferred from anatomical considerations alone apart from actual experiment." In man, the olfactory system assumes a relatively minor role in the total organization of the brain, although olfactory impressions serve as a potent stimulus in the psychomotor sphere. In 1890 Hughlings Jackson and Beevor described a tumour of the right temporosphenoidal lobe which had caused episodic disturbances in the form of olfactory seizures. The tumour was sharply circumscribed and the olfactory nerves were intact. Ferrier had stimulated the hippocampal lobe in monkeys and other animals, and recorded that a peculiar torsion of the lip and nostril occurred on the same side which he believed associated with subjective olfactory sensation. Munk(1880)recorded the case of a dog whose occipital lobes were removed and which thereafter appeared not only blind but also to have lost its olfactory sense. At post mortem the hippocampal gyrus had been destroyed by a cyst. In recent years the olfactory brain has been studied principally from the point of view of comparative anatomy; application of conditioned reflex techniques by W. F. Allen and others has also been made to great advantage.

THE olfactory areas of the brain in lower forms represent the anlage of the neocortex — a point which all comparative anatomical studies have emphasized. In fish, the entire cerebral hemisphere is made up of olfactory cortex and in amphibians the archipallium(pyriform lobe)first makes its appearance. In man, and in higher mammals generally, the neocortex entirely overshadows the olfactory brain, but olfaction contributes in an important manner to the psychic life of the human organism and is frequently subject to derangement from peripheral as well as from central causes. The physiology of the rhinencephalon, however, is largely based on inference drawn from its anatomical relations.

ANATOMICAL CONSIDERATIONS

The olfactory brain consists of two primary divisions:(i)the peripheral embracing the olfactory lobes(olfactory bulb, tract, tuberculum and parolfactory area)and the posterior olfactory lobes, including the anterior perforated substance, the subcallosal gyrus, and the diagonal rhinencephalic gyrus; and(ii)the central parts of the olfactory brain, includ-

ing the hippocampus and limbic lobe, etc. These anatomical subdivisions will be briefly discussed in this order.

Peripheral structures. The olfactory epithelium forms an arch in the roof of the nasal mucosa covered by soft mucus, in which lie the hair cells of the primary olfactory neurons. These neurons form dendrites that pass upward to the olfactory bulb through the cribriform plate of the ethmoid. The olfactory nerves enter the olfactory bulb and there form the superficial fibre layer (fig. 77), which leads to the second layer of the olfactory bulb (glomerular layer). The olfactory bulb is a complex structure histologically, first described in detail by Ramón y Cajal. In addition to a glomerular layer, there is a molecular layer, containing large and small brush cells, which with the mitral cells closely adjacent pass to the deepest or granular layer, the cells of which give rise, along with the axons of the mitral cells, to the olfactory tract. The olfactory bulb is thus a somewhat modified diverticulum of the olfactory brain and retains the laminated structure of the allocortex. The olfactory tracts, thus made up of axons from various layers of the bulb, merge in the tuberculum olfactorium, which forms the olfactory trigone. From the tuberculum, the fibres pass backward into the olfactory cortex proper by way of the lateral olfactory gyrus. Some fibres also pass into the medial olfactory gyrus, which gives rise to the parolfactory area of Broca (which communicates with the gyrus cinguli). The lateral olfactory gyrus brings fibres to the uncinate gyrus and the gyri ambiens and semilunaris (see fig. 77). It also sends fibres to the anterior perforated substance.

POSTERIOR OLFACTORY BRAIN. This is made up of the anterior perforated substance and the subcallosal gyri. The forepart is generally designated the "perforated rhinencephalic gyrus" and the more posterior division is the diagonal rhinencephalic gyrus of Broca already mentioned. Posteriorly, the diagonal gyrus communicates with the frontal end of the hippocampal gyrus.

Cortex of olfactory brain. This, as is well known, includes Ammon's horn (hippocampus) and the following gyri which lie in close proximity to the corpus callosum: hippocampal, dentate, uncinate, intralimbic, callosal and fasciolar. Together these form an almost complete circle (fig. 77), beginning along the medial surface of the temporal lobe, extending backward through the isthmus around the posterior genu of the corpus callosum to form the cingular gyrus, which passes anteriorly around the anterior genu of the corpus callosum deep to the frontal lobe into Broca's field. The cytoarchitectural characteristics of the rhinencephalon have been briefly described in the previous chapter under the allocortex. Following Brodmann's division Lorente de Nó (1934a) recognizes six layers in the hippocampus (Regio entorhinalis of mouse, monkey and man): (i) the plexiform layer, (ii) layer of star cells, (iii) superficial pyramids, (iv) deep pyramids, (v) small pyramids with recurrent axis cylinders, (vi) polymorphic cells. The individual laminae, however, are often difficult to distinguish and in various parts of the rhinencephalon they pass under different names, such as the original four laminae into which were at first divided: (i) stratum moleculare, (ii) stratum radiatum, (iii) stratum oriens, and (iv) alveus. For the details of cytoarchitecture, however, one must consult primary sources, such as Lorente de Nó (1934a&b) and O'Leary (1937).

The connections of the rhinencephalon are not completely established, but certain primary connections are well known. Thus, from the hippocampus a conspicuous tract known as the "column of the fornix" passes directly to the mammillary body of the posterior hypothalamus; fibres from the anterior perforated

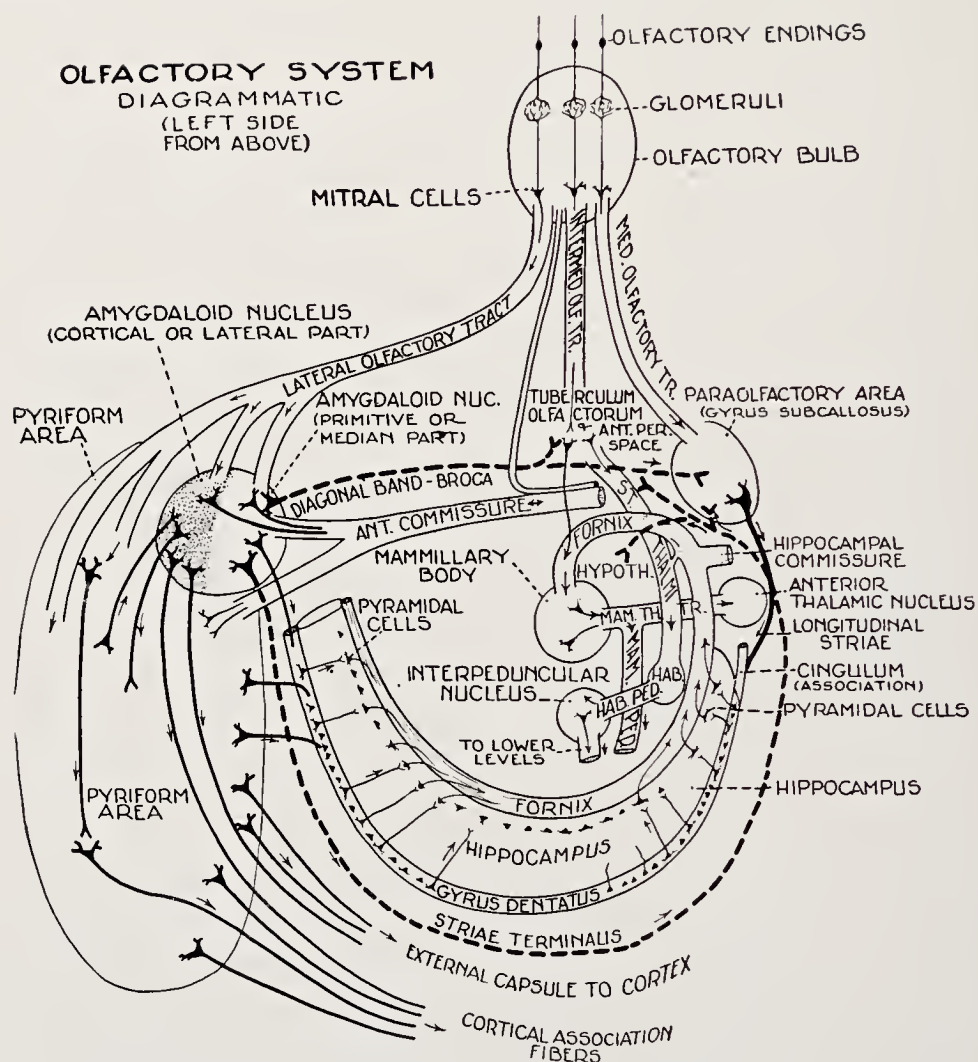


FIG. 77. A diagram of the principal connections of the olfactory system and rhinencephalon (W. F. Allen, *Amer. J. Physiol.*, 1940, 128, 767).

space pass to the habenula ganglion and others to the mammillary body. Some fibres also pass through the cerebral peduncle to the mesencephalic nuclei, *e.g.*, mammillopeduncular, mammillotegmental and habenulopeduncular. The anterior part of the *cingulate* gyrus is also linked with the anterior thalamic nuclei by thalamocortical and probably also by corticothalamic connections. The two halves of the hippocampus are connected by the hippocampal commissures.

GENERAL FUNCTIONS

The physiology of the olfactory brain is, as already pointed out, essentially a matter of anatomical inference.

COMPARATIVE STUDIES. The comparative physiology of the rhinencephalon has been summarized by Judson Herrick(1933)in the following terms:

1. In exteroceptive adjustments the olfactory sense, lacking localization of its own, coöperates with other senses in various ways, including a qualitative analysis of odours and the discrimination between desirable and noxious stimuli, activation or sensitizing of the nervous system as a whole and of certain appropriately attuned sensorimotor systems in particular, with resulting lowered threshold of excitation for all stimuli and differential reinforcement or inhibition of specific types of response.

2. Tissue differentiation within the pallial field began in phylogeny with the penetration into this part of the primitive olfactory area of various systems of non-olfactory projection fibres, resulting in more efficient adjustments(both interoceptive and exteroceptive)to all situations containing olfactory excitation.

3. In the course of differentiation of the cerebral cortex the olfactory system plays the dominant role in primitive types, to be reduced to a subordinate position in primates as the neopallium is expanded and differentiated.

4. At all stages of cortical elaboration an important function of the olfactory cortex, in addition to participation in its own specific way in cortical associations, is to serve as a non-specific activator for all cortical activities. This is a generalized activity of primitive type acting on the neopallial cortex as a whole, lowering its threshold or increasing its sensitivity, or, in the case of noxious stimuli, exerting inhibitory influence.

This type of non-specific activity is one of the major functions of the olfactory cortex, though all parts of the neopallium also exhibit it to some degree. It comes to expression in overt behaviour, learning capacity, memory, etc., as a differential influence upon other cortical and subcortical functions of those exteroceptive sensorimotor mechanisms whose specific patterns of response show well defined anatomical and physiological localization. Having no localization pattern of its own, it may act in two ways: first upon other exteroceptive systems whose localized mechanisms are adapted to execute adjustments where external orientation is demanded, and, second, upon the internal apparatus of general bodily attitude, disposition and affective tone, the "intimate senses" of Starbuck.

EFFECTS OF STIMULATION. Information concerning olfactory functions has been derived from the experiments of Rioch and Brenner(1938). They removed the entire neocortex plus cingulate gyrus, leaving intact the isocortex, *i.e.*, the pyriform lobes and the tuberculum olfactorium. Several months later these chronic decorticated preparations were stimulated faradically under dial anesthesia. Stimulation of this basal olfactory area provoked a variety of responses, having one feature in common, "that they appeared to be related to smelling and eating. In five of the seven cats stimulation in this region was accompanied by marked salivation. Other responses included irregular chewing, swallowing, and chop-licking(tuberculum olfactorium). From the pyriform area there occurred jerking movements of the head back and forth, a sharp

inspiratory movement as though sniffing, dilatation of the pupils, and, if the stimulus was prolonged, also irregular chewing and swallowing. From a more medial point retching occurred and from one animal tongue movements." Similar behaviour has been noted by Klüver and Bucy(1939)after bilateral temporal lobe ablation.

These reactions are similar to the *spontaneous behaviour* exhibited by these chronic decorticated animals. Rioch and Brenner conclude, "that the central representation of the feeding reactions associated with smell is in the basal olfactory brain, possibly chiefly in the pyriform lobes. A comparison of the results obtained in the present animals with functional anatomical studies of Magoun, Ranson and Fisher(1933), and with the analysis of 'cortical' chewing in the rabbit and guinea pig by J. Rioch(1934)clearly indicates that there are at least two separate forebrain mechanisms which may activate the trigeminal, facial and hypoglossal centres in the hind-brain." A similar conclusion has been reached by Swann(1934)on the basis of his discrimination studies(cf. also Brown and Ghiselli, 1938; Woolsey, *et al.*, 1943).

In the macaque Wilbur Smith(1941)has obtained similar responses, also vocalization, from stimulating the cingulate gyrus. The response "most frequently elicited consists of a low guttural sound, emitted once if the application of the stimulus is of brief duration, but repeated several times if the stimulus is applied for a longer time. In some instances a sound of higher pitch is obtained. Vocalization may occur alone, but in its fully developed form it is part of a complex act simulating emotional expression, and is characterized by opening of the eyes, dilatation of the pupils, opening of the mouth, retraction or protrusion and rounding of the lips, and vocalization. When the stimulus is applied the animal appears to awaken, when it is discontinued the eyelids close and the animal appears to fall asleep. Bilateral extirpation of the excitable area does not result in loss of the ability to vocalize.

"Respiration changes markedly in character during the vocalized response, but in addition to this change, stimulation has a pronounced inhibitory effect upon respiration in the absence of vocalization. Furthermore, excitation often produces a marked inhibition of movements of the extremities, any movement in process of execution is stopped, and relaxation of the muscles ensues. A striking demonstration of the inhibitory power of this area is evidenced by the finding that the struggling which ordinarily ensues when the ether cone is applied to the lightly anesthetized animal is completely prevented or abolished by application of the stimulus just before the anesthetic is applied."

CONDITIONED REFLEX STUDIES. In a series of notable papers W. F. Allen has studied the effects of ablating various parts of the olfactory brain, as well as of the cerebral cortex, upon the establishment of olfactory conditioned reflexes of dogs. In an early paper of the series(1937)he estab-

lished that clover, lavender, anise, asafetida, benzol and xylol evoke conditioned reflexes solely by way of the olfactory nerves, and the possibility of conditioning is abolished when the olfactory nerves are severed. Camphor, eucalyptus, pyridin, butyric acid, phenol, ether, chloroform, and "mange cure" evoke reflexes over the trigeminal nerve, as well as the olfactory. These more pungent, irritating substances therefore were excluded in subsequent studies of olfactory conditioning.

Allen(1938) finds that bilateral ablation of the motor area prevented acquisition of olfactory reflexes involving a leg and that discrimination responses between, *e.g.*, cloves and asafetida, became impossible. More elaborate discriminatory tests involve establishment of a negative conditioned response to asafetida and conditioned differentiation which involved a decision in 7 sec. whether to respond positively to cloves or negatively to asafetida was abolished by bilateral extirpation of the frontal lobes(1940). Such ablations, however, did not prevent dogs blind-folded from distinguishing a bag of meat from other less attractive parcels. Bilateral ablation of the pyriform-amygdaloid areas(1941) causes similar elimination of discriminatory conditioning, but as with the frontal lobe ablations, there was no difficulty in the dog recognizing meat when blind-folded. Allen concludes that, whereas the pyriform-amygdaloid complex is an important olfactory centre in the dog, it does not represent the sole centre for detecting minute differences of odour. Inclusion of the hippocampi with the pyriform-amygdaloid ablations causes no additional deficit(1941). Finally, bilateral destruction of the pyriform-amygdaloid-hippocampal complex had no effect on *taste* responses evoked from solutions of sugar, salt, quinine or acetic acid(ch. xix). Allen's studies represent the first systematic attempt to unravel the physiology of the olfactory system in higher animals, and it is earnestly hoped that this profitable line of investigation will be actively continued.

CLINICAL STUDIES. Recently quantitative studies have been made of olfactory functions by the new olfactory osmetric technique of Elsberg (1935) and his collaborators. He uses a test bottle of fixed size, a special nose piece, and injects into the olfactory passages a measured volume of olfactory stimulus by a sudden puff of air. Threshold is established by determination of the minimum identifiable odour(M.I.O.). This is expressed in terms of the number of cubic centimetres of air containing a known concentration of olfactory stimulus; by this means "a mono-

rhinal acuity" is established. When this value is compared with the number of cubic centimetres needed to recognize an odour when injected into both nares, a value is obtained which is designated "the olfactory coefficient." This determines the birhinal acuity. In the presence of peripheral or central lesions, these values undergo large variations.

SUMMARY

The principal connections of the olfactory brain are summarized in figure 77. Physiological studies suggest that feeding reactions associated with smell are mediated by the basal part of the olfactory brain, chiefly in the pyriform lobes. Lesion of any part of the olfactory projection diminishes but does not wholly abolish olfactory acuity. Bilateral ablation of the pyriform-amygdaloid complex causes abolition of olfactory conditioned reflexes, but no impairment of the sense of taste.

Adrian(1942), Rose and Woolsey(1943)and W. F. Allen(unpublished)have explored the potential changes in the cerebral cortex following stimulation of the olfactory bulbs. Rose and Woolsey employed faradic stimulation and detected conspicuous electrical reactions in the olfactory tract, the prepyriform, the periamygdalar and the entorhinal areas of the hippocampal gyrus. No responses were detected in the retrosplenial area or the olfactory tubercle. Allen has obtained similar reactions in the above areas following natural stimulation of the olfactory epithelium brought about by insufflations of xylol, cloves and asafetida. He has also established an important physiological inter-relation between the pyriform lobe and the prefrontal areas: "Single shock stimulation of the pyriform lobe evoked potentials from the ventro-lateral portion of the prefrontal area and antidromically from the olfactory bulbs, but not from other cortical areas. No spikes were recorded from the prefrontal area following stimulation of the olfactory bulbs or from stimulating the pyriform lobe of one dog after areas 8, 9 and 10 had been under cut from the rear."

XVII

CEREBRAL CORTEX: THE OCCIPITAL LOBES AND VISUAL SYSTEM *

HISTORICAL NOTE

In 1823 Flourens first established experimentally that vision depends upon the integrity of the cerebral cortex. Following ablation of one cerebral hemisphere (pigeons, rabbits and dogs) the eye on the opposite side appeared blind, and following bilateral removal of the hemispheres blindness was complete. In 1830 Bouillaud confirmed the observations which were further substantiated by Magendie (1841), Longet (1842) and others. These early investigators pointed out that despite gross evidence of blindness the pupils constricted in the presence of bright light. The first to localize visual function in the posterior part of the cerebrum was Panizza (1855). He had studied the brains of two patients, one of whom was blind following an apoplectic stroke, and, after observing the lesions, concluded that the parieto-occipital area was the part of the cortex essential for vision. He put his hypothesis to experimental test on dogs, finding that they became blind when only the occipital region was ablated. Panizza's observation was forgotten, and in 1874 Hitzig independently reported similar experiments on dogs. The following year Ferrier extended the experimental work to monkeys, but concluded that the visual centre lay in the angular gyrus. This later led him into a controversy with Schäfer (1888a) who on the basis of ablation experiments in monkeys concluded that the occipital lobes contained the primary visual cortex (Sanger Brown and Schäfer, 1888). Prior to Schäfer's studies, it was always the opposite eye that was described as blind, but Schäfer stated that his monkeys, after unilateral occipital ablation, suffered a "homonymous hemianopsia" of the field of vision opposite to the ablation (Schäfer, 1888b; Thompson and Sanger Brown, 1890).

More precise localization of the visual area had to await anatomical study. Munk (1880), however, had suggested before Schäfer that the visual area was restricted to the superior surface of the occipital lobes (dogs). The conclusion was vigorously attacked by Luciani (1884), who pointed out that some degree of visual disturbance occurred with all cerebral operations, and that therefore visual function must have a diffuse representation. With improvement in surgical methods more circumscribed lesions were made both in dogs and monkeys (*e.g.*, Schäfer), and this, correlated with human pathological material of Henschen (1890) and Wilbrand (1890), caused the visual area to be restricted to the area striata, defined by the students of cytoarchitecture. The first experimental proof of this more precise relationship in animals was offered by Minkowski's studies on dogs in 1911, those of Polyak on monkeys (1933) and Holmes' in man (1918). Minkowski (1917) was unable after lesions of parts of the cortex other than area 17 to produce sig-

* I am indebted to Dr. Donald Marquis for assistance in the revision of this chapter.

J. F. F.

nificant visual disturbance. Anatomical evidence then followed, establishing the visual projections from the lateral geniculate bodies to area 17 (see ch. xv).

THE VISUAL PROJECTIONS

PRIMARY NEURONS. The primary neurons of the visual system take origin in the eighth, or "ganglion," layer of the retina (fig. 78). These neurons have extensive connections in the retina itself and with other

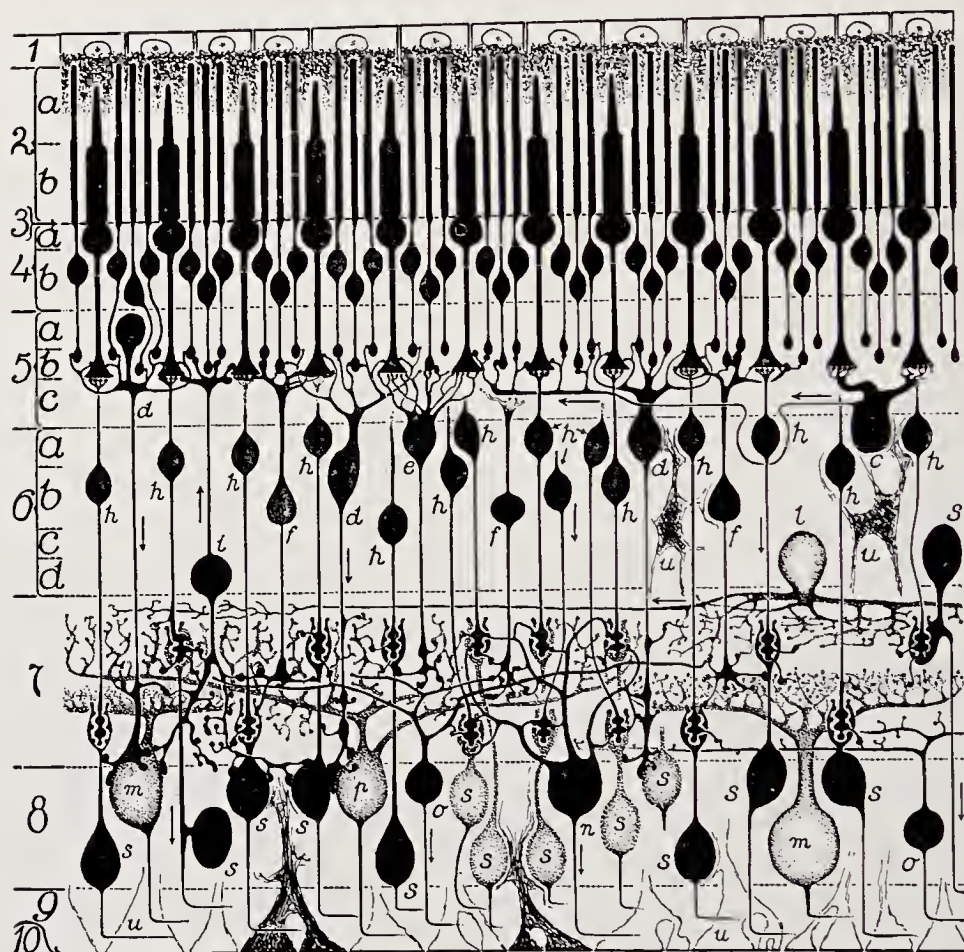


FIG. 78. Diagram of nervous elements of retina in a monkey, based on Golgi impregnations. The scheme shows chief characteristics of retinal nerve cells and their position. Layers are: (1) pigment epithelium; (2a) outer segment of rods and cones; (2b) the inner segment of rods and cones; (3) outer limiting membrane; (4) outer nuclear layer; (5) outer plexiform layer (cone-pedicles and rod-spherules); (6) inner nuclear layer; (7) inner plexiform layer; (8) ganglion cells (origin of primary visual projections); (9) layer of optic nerve fibres; (10) inner limiting membrane; *c*, horizontal cells; *d*, *e*, *f*, *h*, bipolar cells; *i*, *l*, "amacrine cells"; *m*, *n*, *o*, *p*, *r*, *s*, ganglion cells (S. Polyak, *The Retina*, Univ. of Chicago Press, 1941).

neurons in the retinal complex, more particularly with the primary visual receptors, the rods and cones by way of the bipolar cells of layer 6. The rods are scattered diffusely throughout the retina, except in the "macula" or *fovea centralis*, and are concerned with night sight and with peripheral vision. The macula is occupied entirely by cones and is concerned with so-called "central vision" — the area of greatest visual accuracy ("acuity").

Retina. One cannot here describe the complex histology of the primate retina. The recent work of Polyak (1941) indicates that it is made up of ten clearly recognizable layers as shown in figure 78, based on the macaque retina. That of the chimpanzee is similar. Interconnection of the cones with other structures in the retina is less extensive than that of the rods; the cones generally project directly to a single ganglion cell in the eighth layer, thus tending to have a 1:1 ratio with the ganglion cells that give rise to the primary visual projections. The rods, on the other hand, have an extensive interconnection in the retina itself and appear to be greater in number than the primary neurons which carry their impulses to the nervous system. It should be borne in mind also that the retina is normally *inverted*, the rods and cones pointing inward toward the brain.

The axons of the primary visual neurons pass a short distance rostrally in layers 8 and 9, and in layer 9 turn at right angles across the superficial surface of the retina (fig. 78), sweeping toward a common central focus to form the optic nerve. In man and primates having binocular vision, approximately half of the fibres in each optic nerve cross in the optic chiasm to the opposite half of the brain. The fibres which cross come from the nasal half of each retina and hence are those responsible for the *temporal* field of vision (fig. 79). Each optic tract thus formed from the optic chiasm is made up of the fibres from the nasal half of the opposite retina and the temporal half of the ipsilateral retina. Lesions of the optic tract, therefore, cause blindness in the contralateral visual field, and such a visual deficit is spoken of as "homonymous hemianopsia."

If, however, the optic chiasm itself should be divided in the *midsagittal* plane, the fibres from the nasal half of each retina would be severed, and the resulting visual defects would be in the temporal fields of vision. Such defects are known as "bitemporal hemianopsia"; they are often caused by expanding tumours of the pituitary body, which compress the crossing fibres of the chiasm earlier than the more laterally situated uncrossed fibres. If the optic chiasm is compressed *laterally*, as sometimes happens in man when the internal carotid arteries become sclerosed and calcified, the fibres from the temporal halves of each retina will be compressed and the result will be a binasal field defect.

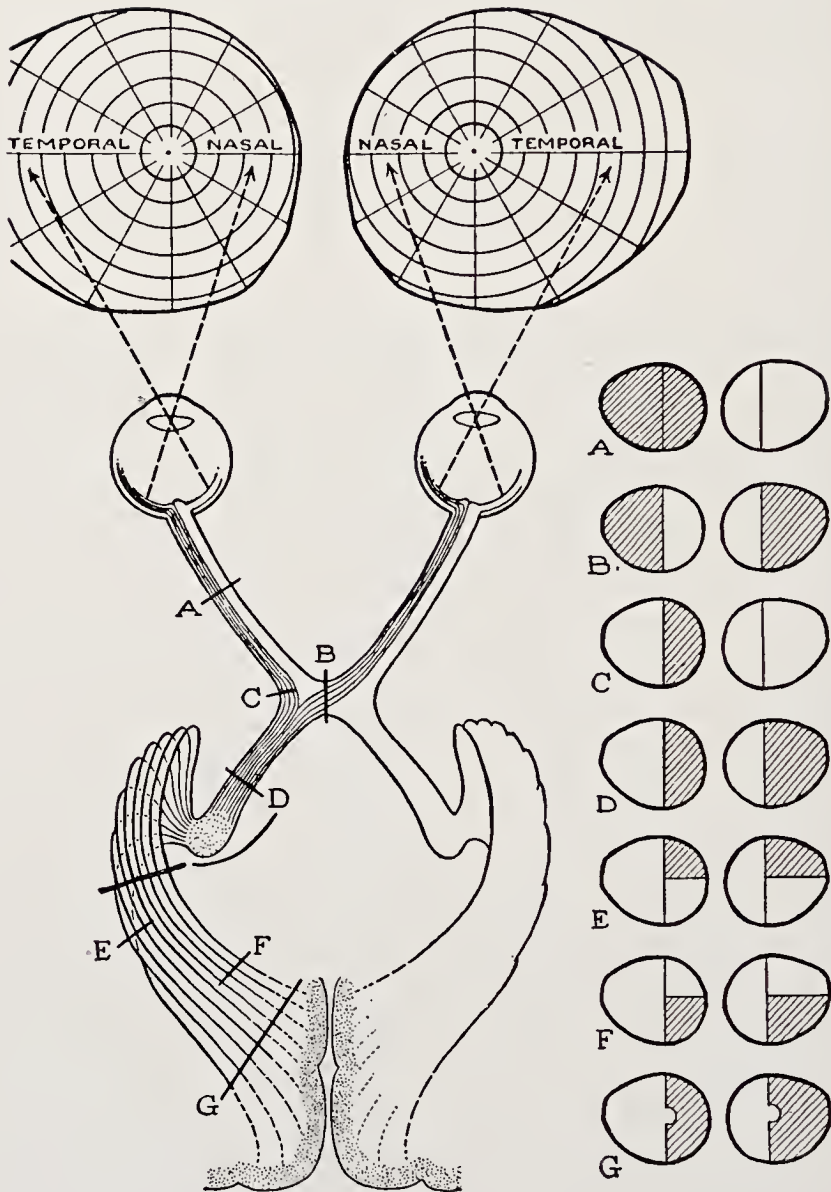


FIG. 79. Optic pathway showing how lesions at various points will affect fields of vision. Shaded areas in small perimetric fields on right correspond to lesions marked in left hand figure. A, Complete blindness in left eye. B, Bitemporal hemianopsia (pituitary tumours). C, Nasal hemianopsia of left eye. D, Right homonymous hemianopsia (seen after section of optic tract, or after interruption of geniculocalcarine projection). E and F, Right upper and lower quadrant hemianopsias. G, Right homonymous hemianopsia with preservation of macular vision (encountered with large lesions of calcarine cortex) (Homans, *A text-book of surgery*, 5th ed., C. C. Thomas, 1941, p. 539).

Within the optic nerve, chiasm and optic tract, a precise dorsoventral organization of the fibres is maintained up to their termination in the lateral geniculate bodies. Thus, fibres from the ventral half of the retina (superior visual field) pass in the midventral surface of the chiasm and are the first to be affected by an expanding lesion in the sella turcica — hence the early appearance of superior quadrant field defects in cases of pituitary tumour. Fibres from the dorsal half of the retina pass in the dorsal part of the chiasm, and are therefore less quickly affected by chiasmic compression from within the sella. The macular fibres underlying central vision pass in the lateral part of the chiasm to form a large superior-lateral fasciculus of fibres in the optic tract. The fibres from the ventral half of the retina pass lateral to the macular fibres (fig. 80A), whilst the fibres from the superior half of the retina pass medial to the macular fibres in the optic tract (Biernond, 1929; Brouwer and Zeeman, 1925, 1926).

The fibres which are concerned with light reflex pass along the medial surface of the optic tract and, instead of terminating in the lateral geniculate body, pass along its medial border and thence to the pretectal region (ch. XI).

Lateral geniculate bodies. The optic tract courses directly to the thalamus, where it terminates on successive laminae of the lateral geniculate body (ch. XIV) to form synaptic connections with the second order neurons of the visual system; these pass from the geniculate body directly to the area striata of the occipital lobe. The spatial relationship of the fibres in the optic system has been studied by Brouwer (1926), Le Gros Clark and Penman (1934; see also Le Gros Clark, 1941). Brouwer and Zeeman (1926) and Biernond (1929) made small lesions in the retina of monkeys, cats and rabbits and followed the resulting degeneration from the optic nerve to the lateral geniculate body. In this way, a precise point-to-point relationship was established between the retina and the lateral geniculate (fig. 80B). Curiously enough, the destruction of primary visual neurons in the retina causes the cell bodies of secondary neurons (in geniculates) to degenerate — a phenomenon known as “transneuronal degeneration”; thus, a lesion in a given spot of the retina will cause a predictable *transneuronal* degeneration in a cluster of cells in the external geniculate (Le Gros Clark, 1932). Similarly, lesions restricted to area 17 give rise to a correspondingly predictable chromatolytic lesion in the external geniculate body (Polyak, 1934). This latter degeneration is “retrograde” since it involves cell bodies whose axons have been actually severed (see Talbot and Marshall, 1941).

As already indicated, the spatial organization of the optic tract fibres in relation to the retina is preserved in the external geniculate body. Thus the superior and central two-thirds of the lateral geniculate body is taken up by macular projection (fig. 80B), whereas the medial ventral quadrant is made up of fibres from the superior half of the retina, and

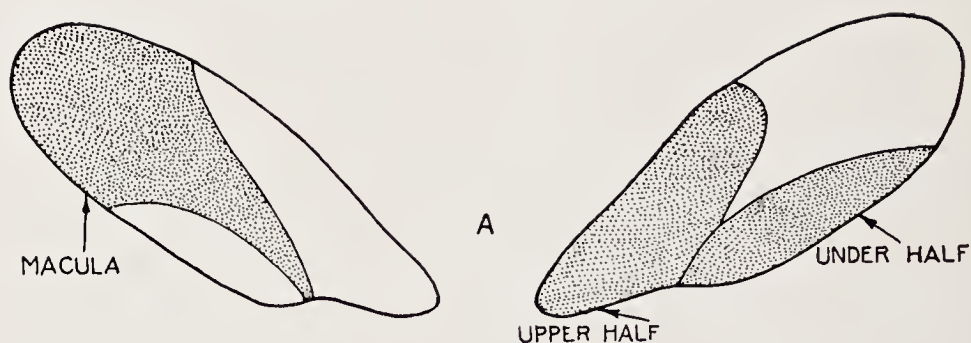


FIG. 80A. Optic tract of a monkey showing position of fibre degeneration after lesion of macula(left), and after lesions of upper and lower halves respectively of peripheral retina(right)(Brouwer and Zeeman, *Brain*, 1926, 49, p. 25).

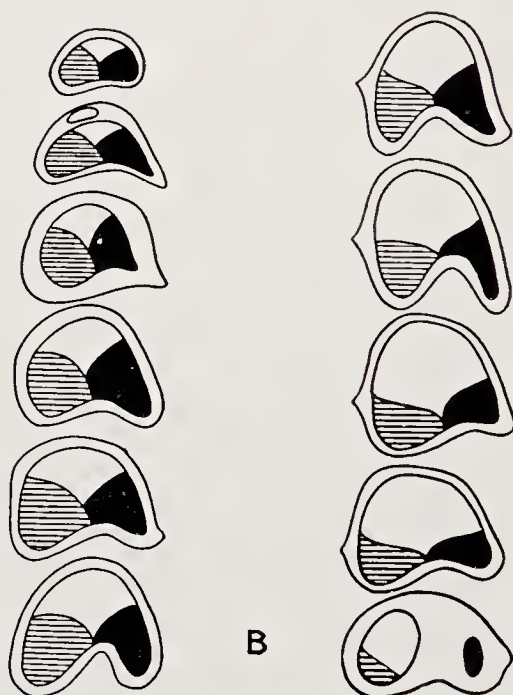


FIG. 80B. Lateral geniculate body of monkey showing relative position of projections from macula(white), upper peripheral retina(black)and lower peripheral retina(hatched); sample section from before backward. Compare with figure 80A(after Brouwer and Zeeman, *Brain*, 1926, 49, p. 26).

a lateral ventral quadrant of fibres from the ventral half of the retina, exclusive of the macula. It was mentioned in chapter xv that the lateral geniculate body is composed of successive laminae, and it was Minkowski(1913)who first pointed out that the fibres from each retina terminate on alternate laminae of the geniculate.

SECONDARY NEURONS. The secondary neurons of the visual system form the optic radiation, or, more accurately, the "geniculocalcarine" tract. Archambault(1909)and Adolph Meyer(1907)independently observed that the external sagittal stratum of the optic radiation passed forward and around the inferior part of the lateral ventricle and into the white matter of the temporal lobe beneath the medial temporal convolution(fig. 79). Lesions of the temporal lobe, therefore, frequently involve these fibres and thus produce a homonymous defect in the upper quadrant of the field of vision(fig. 79E)(Cushing, 1922). The optic radiations then pass directly to the calcarine cortex(area 17).

TOPOGRAPHY OF VISUAL CORTEX. Although the spatial organization of fibres in the optic pathways and in the lateral geniculate body is well known, there is still some uncertainty about topographical localization within the calcarine cortex itself. There are three mooted points:(i) region of termination of fibres from macula,(ii)representation of peripheral retina, and(iii)the question of bilateral macular representation.

Macular representation(central vision). All are agreed that the majority of macular fibres in man and monkey project to the occipital pole, *i.e.*, the posterior part of area 17. Thus, when this part of the cortex is destroyed experimentally in monkeys or in chimpanzees, the superior two-thirds of the ipsilateral geniculate body(to which the primary neurons of the macula project; figs. 81 and 82)entirely degenerates, and, as far as one can determine from animal experimentation, the animal exhibits a hemiaropsia of central vision. However, it is virtually impossible to determine visual fields with accuracy in animals, and one is therefore obliged to turn to clinical evidence. In a series of cases reported by German and Fox(1934), in which radical ablations of the occipital lobes were carried out in the treatment of brain tumours, there was one case which showed sparing of macular vision after all except the rostral end of the area striata(calcarine fissure)had been removed. They concluded from this that in man, though macular representation is predominantly in the occipital pole, there are some macular fibres distributed more anteriorly. In Brouwer's(1930)case, in which there was a small throm-

botic lesion in the middle part of the calcarine fissure, central vision was also spared in the presence of an otherwise almost complete hemianopia. Holmes and Lister (1916), in a gunshot wound of the occipital pole (a case thought to be complementary to that of Brouwer's), believed that they had demonstrated a large central scotoma, *i.e.*, macular blindness, although the anterior part of the visual area remained intact. Brouwer's case and various experimental studies indicate that lesions of the

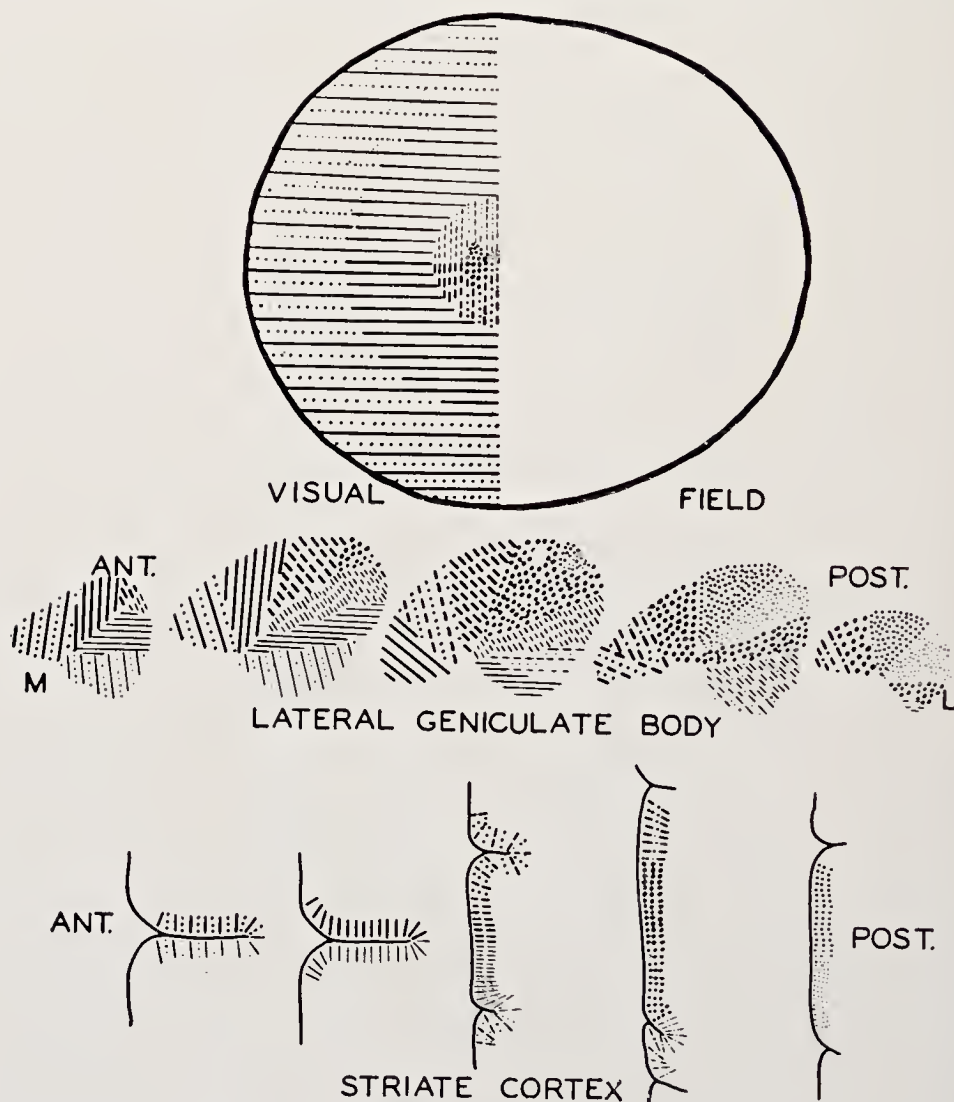


FIG. 81. Schema to show projections of lateral geniculate body upon striate cortex of chimpanzee and retinal projections upon lateral geniculate body and striate cortex (Walker and Fulton, *Brain*, 1938, 61, 250).

rostral end of the calcarine fissure may give rise to disturbances of peripheral vision, and that they may also cause degeneration of the ventral quadrants of the lateral geniculate body (fig. 81). Holmes and Lister found that the superior half of each retina is represented in the dorsal and the lower half of each retina in the ventral part of the calcarine cortex.

The *sparing* of the macula reported by Fox and German (1936), Penfield, Evans and MacMillan (1935) and recently by Halstead, Walker

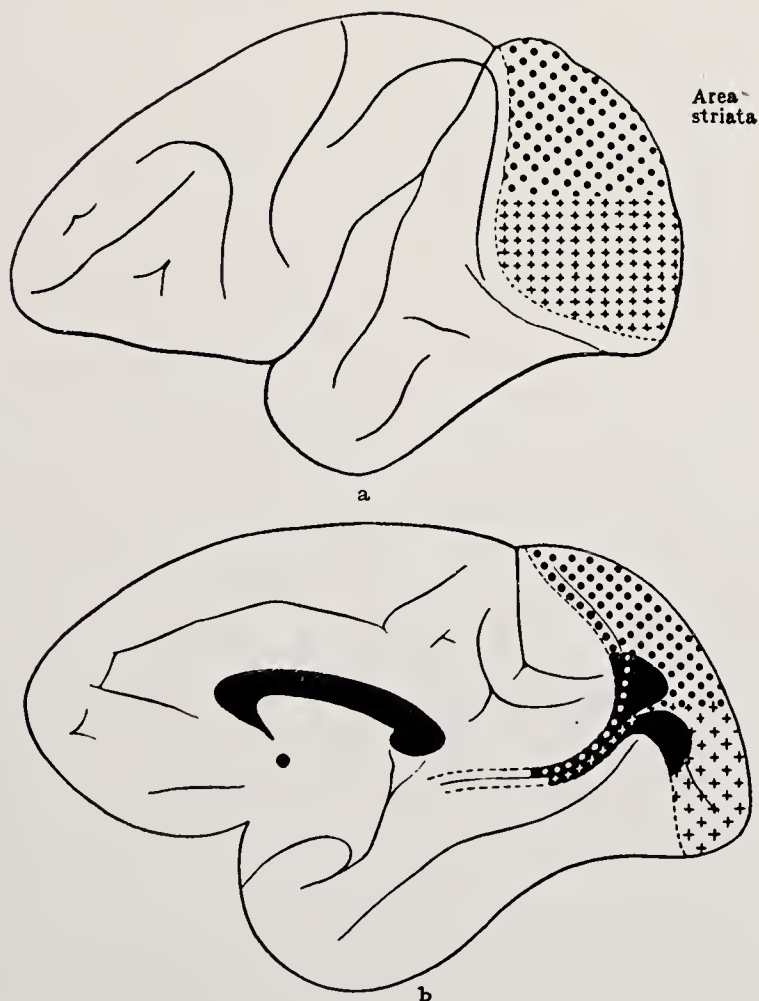


FIG. 82. Occipital lobe of monkey showing areas of projection of macula (dots, dorsal macular quadrant; crosses, ventral macular quadrant), and peripheral retina (black). A, Lateral surface of hemisphere. B, Medial surface of hemisphere. Note overlapping between peripheral and macular projections (after G. J. van Heuven, *Dissertation*, Amsterdam, 1929).

and Bucy(1940), following extensive ablation of the occipital lobes, has been attributed to bilateral representation of the macula in the striate cortex. Thus, for central vision, a type of bilateral representation has been postulated similar to that existing in the parietal lobes for pain sensibility. In the case of the parietal lobes, the bilaterality of representation has a sound anatomical basis in the uncrossed fibres of the spinothalamic tracts which project to the posteroventral nuclei; but in the case of the visual system there is no anatomical evidence of bilateral representation (cf. Polyak, 1941; Putnam, 1934). When the occipital lobe is removed completely in monkeys, in chimpanzees, and in man, the external geniculate body on the same side undergoes complete degeneration, *i.e.*, there is no evidence that it receives or sends fibres to the occipital lobe on the opposite side. Putnam and Liebman(1942) summarize the present evidence concerning macular sparing as follows:

The preponderance of evidence is in favor of an extremely large representation of central vision at the posterior end and in the depths of the calcarine fissure. It is possible that central vision has some representation even at the anterior end of the fissure and if so doubtless in the portion adjacent to the ventricle.

There is no satisfactory anatomic evidence of a callosal bundle uniting one geniculate body with the striate cortex of the opposite side, and there is considerable evidence that such a decussating pathway does not exist. The clinical cases on the basis of which such a decussating pathway has been postulated are better explained by other hypotheses.

Many cases are on record in which a homonymous hemimacular scotoma has existed, but in only 1 of these has the brain been examined in serial sections. The lesion was found at the tip of the occipital lobe. In all cases, the lesion has been traumatic and has presumably injured the optic radiation.

Lesions of the anterior portion of the striate area on one side produce a contralateral hemianopia with a large remnant of central vision. Lesions of the tip of the occipital pole produce a hemianopia with irregular boundaries, sometimes with only 1 or 2 degrees of central vision. Neither type of central field is actually "macular." Total or subtotal lesions of one occipital lobe may produce either a complete hemianopia or one with varying traces of central vision.

The persistence of central vision in cases of a lesion of the occipital lobe may be due to any one of several factors. One is the extensive representation of macular vision, probably occupying over half the area of the visual cortex and possessing a blood supply from three sources.

Another explanation of the tiny remnants of central vision following extensive lesions is that there is a constant physiologic shift of fixation, so that an object in the hemianoptic field but near the fixation point may be brought into view. In some cases, there is evidence of the formation of a new fixation point, within the preserved field.

Finally, it seems likely that a certain degree of visual perception may be taken over by lower visual centers after occipital lesions, as clearly occurs in monkeys.

Many believe, in view of these considerations, that the alleged sparing of the macula in cases of removal of the occipital lobe is due to incomplete destruction of the striate cortex. Foerster(1929), moreover, has reported a case of occipital lobectomy in which there was no macular sparing, as have Halstead, Walker and Bucy(1940).

The course followed by the optic projections leaves little basis for dispute. The best evidence indicates that macular representation in the cortex, far from being diffuse, is actually more precisely organized than any other sensory system in the body; and that a small lesion in the occipital cortex gives rise to a correspondingly circumscribed defect for object vision in the contralateral visual field.* The cases with small lesions which have come to autopsy are still few, but their number is sufficiently impressive, especially those reported by Holmes and Lister, Holmes, Brouwer, Foerster, to make one entirely confident that a precise point-to-point relationship exists between the retina and the occipital lobe without significant spatial overlapping.

PHYLOGENY OF VISUAL FUNCTION

The activities of the occipital lobes in visual function in man cannot be fully understood without some knowledge of the comparative physiology of visual function. It has long been recognized, especially by comparative anatomists, that the central nervous system exhibits an orderly development in phylogeny characterized by the shifting of function from lower towards higher centres("encephalization"), and nowhere is the growth of dominance of the higher centres more strikingly illustrated than in the evolution of visual function. To Marquis(1934, 1935) we owe the recent elaboration of the phylogenetic concept of visual function. The following brief review is based on his own work and kindred studies by other investigators.

* Lorente de Nó(1934b) has discussed the point-to-point relationship in the visual system and stresses the fact that anatomically each retinal impulse may influence many points on the cortex because of arborization of neurons in the retina(fig. 78), geniculates and cortex, but that physiologically the precise relationship may still hold. Thus he says (pp. 172-173): "Each point of the retina is projected into a large area of the cortex, because the arborizations, protoplasmic and axonal are extensive, and therefore the impulses set up in any point of the retina may be transmitted to a large area of the cerebral cortex. However, assuming that the neuron is a summation apparatus, which reaches threshold excitation only when a certain number of its synapses are active, it becomes evident that physiologically the projection of the retina on the cerebral cortex may be point-like." See also Talbot and Marshall(1940); Hartline(1940).

In lower as well as in higher animals, the connections established in the tectum suffice for primitive optic reflexes such as the reaction of the pupils to light. These reactions, even in man, may occur in the absence of the cerebral cortex. The cerebral cortex plays a part, not in the primary visual reflexes, but in the spatial elaborations of visual function. In *fish* and possibly in the *amphibia*, the optic system has no significant connection with the forebrain and removal of the cerebral hemispheres produces no detectable impairment of vision (Meader, unpublished). In *reptiles* and *birds*, the beginning of the cerebral visual projection has been established, but the tectum remains, as in the fish and *amphibia*, the principal visual centre, and, according to Schrader (1889), complete removal of the forebrain results in almost no visual defects. This has been confirmed by other investigators.

In *rodents*, particularly the rabbit and the rat, the visual cortex becomes definitely localized in the occipital lobes, and lesions of the colliculi or tectum give no evidence of visual defect (Ghiselli, 1937). The studies of Lashley on the rat indicate that removal of the visual area destroys pattern vision, but subcortical activity is sufficient to enable the animal to appreciate differences of light intensity in an almost normal manner, to avoid obstacles, and to recognize food by sight. Thus, a rat whose occipital lobes have been removed has useful vision and could not be described as blind.

Marquis' (1934) work on *dogs* indicates that when the occipital lobe is bilaterally removed the animal appears blind, moving cautiously and slowly when in unfamiliar surroundings, exploring carefully with its paws, especially when going up or down stairs. However, the dog retains the capacity to discriminate differences of light intensity with but little impairment, so that animals in which these discrimination habits have been well developed prior to operation require only a few weeks to reestablish the habit; the dog is then capable of distinguishing between differences in light intensity virtually as small as before the occipital lobes were removed. Simple conditioned responses to light established prior to operation are retained without any retraining (Marquis and Hilgard, 1936; Wing and Smith, 1942). Object vision, on the other hand, is entirely destroyed. In the *cat*, the same holds true (Smith, 1937), but the cat is a night-roving animal and after the occipital lobes have been removed some object discrimination may be possible at intensities comparable to those required for night vision. Optic nystagmus, induced

by rapidly moving vertical stripes in the field of vision, is not impaired although no reaction is made to a single moving stripe or object (Smith, Kappauf and Bojar, 1940).

In the *monkey*, there appears to be virtually no serviceable vision after bilateral removal of the occipital lobes (Klüver, 1936). Object vision is entirely lost, but a primitive light discrimination of a crude type can be demonstrated by sensitive conditioned reflex techniques and is of sufficient intensity to make the animal aware of shadows passing across its field of vision (Marquis and Hilgard, 1936).

Klüver (1941) has shown that such a monkey cannot discriminate between different sizes or brightnesses, but reacts only to the total quantity of light. Performance is greatly impaired under conditions of daylight illumination compared with dark adaptation, and the relative visibility of lights of different wavelength conforms to the customary scotopic luminosity curve.

It is stated that *man* (cf. Marquis, 1934, p. 573), when his occipital lobes are destroyed, is completely and permanently blind and has no light perception whatsoever; pupillary reaction to light, normal motility and retinal structure remain. So far 9 cases of complete blindness from bilateral cerebral lesions have been reported. It is undoubtedly significant that the chimpanzee appears to behave more like man than the monkey (Spence and Fulton, 1936), but as yet no chimpanzee has been observed in which the area striata has been completely removed.

It is thus clear that the elaborate spatial organization of the anatomical projections from retina to the occipital lobe makes possible spatial perception (object vision); the known accuracy of visual perception would be otherwise unthinkable. The problem of binocular and monocular vision, colour and night vision, in relation to perception of distance, falls into the category of special sense physiology and does not concern us in this volume. It should be pointed out, however, that in animals where the visual axes overlap, perception of depth is facilitated through the differing angles of the central axes of vision in the two eyes. This again calls for projections with highly developed spatial organization.

AREAS 18 AND 19

Unfortunately, few experimental studies of areas 18 and 19 are on record. Complete ablation of the region is likely to interrupt the optic radiations to area 17, and hence produce homonymous hemianopsia. Ferrier

(1875) was misled in his early studies of the angular gyrus, because in his zeal to produce a complete ablation, he succeeded in severing most of the optic radiation, and on account of this was led to the erroneous conclusion that the supramarginal gyrus (area 19) was the visual cortex. From clinical observations it is likely that areas 18 and 19 are concerned primarily with visual association — area 18 with intraoccipital associations immediately concerned with the organization of the visual image (*i.e.*, adjustments to proprioceptive impulses from the eye muscles, etc.; Holmes, 1918b), and area 19 with visual associations involving the other sensory and motor areas of the cortex (Horrax, 1923). Visual disorganization (such as defective spatial orientation, monocular diplopia and other visual distortions described by Riddoch, 1917a, 1935, and Holmes and Horrax, 1919; see also Brain, 1941) are also due to lesions of the visual association areas: when the lesion is unilateral, the visual distortion is confined to the homonymous half-field. Visual hallucinations, especially those involving highly organized visual episodes, occur with tumours which compress area 19. Many cases of this sort have been described from Cushing's clinic and are particularly common during the stages of recovery from a hemianopsia after a tumour has been removed from this region (Horrax and Putnam, 1932).

Failure to interpret the written word ("alexia") may also occur following lesions of area 19 of the left hemisphere in right handed individuals (see next chapter).

Details of the physiological organization and interrelation of areas 17, 18 and 19 have been explored by Bonin, Garol and McCulloch (1942) through analysis of cortical electrograms following local strychninization (fig. 83). Area 19, which receives impulses from the entire cortex, and which presumably is concerned with integration of the visual with other projection systems, is designated the "preoccipital" area. Area 18, the "parastriate region," receives impulses only from area 17, the striate cortex. They summarize their observations as follows:

"The occipital lobe of macaque and chimpanzee bears three functionally distinct areas for which the names striate, parastriate and preoccipital are proposed (fig. 83).

1. Strychninization of the striate area leads only to local firing within that area and to firing of the parastriate area. Visual stimuli lead to prompt and large 'on' and 'off' effects in its electrocorticogram. It is well characterized by its histological structure from which its name is derived.

2. Strychninization of the parastriate area leads to widespread firing within this area, to firing into a circumscribed part of the striate area in the vicinity of

the point of strychninization, to firing of the preoccipital area and to firing of the cortex on the inferior temporal and part of the middle temporal convolution. Strychnine spikes also appear within the parastriate area of the opposite hemisphere. Visual stimuli lead in the parastriate area only to the appearance of belated 'ripples.' Its anterior margin is histologically ill-defined, and lies anterior to the position given on cytoarchitectonic maps.

"3. In the preoccipital area strychninization leads to only local firing restricted to the same hemisphere. Its strychninization leads, however, to a suppression of the electrical activity of the cortex which spreads slowly over both ipsi- and contralateral hemisphere. It is histologically ill-defined, but there is good reason to assume that it extends into the intraparietal sulcus and that it is there identical with the cortex described as the 'visuosensory band β .'"

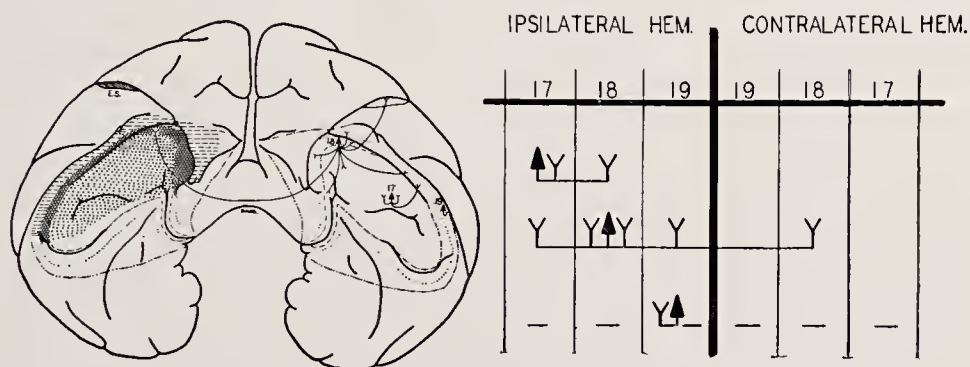


FIG. 83. *Left*, Diagram of occipital poles of macaque showing areas 17, 18 and 19 as determined by electrical response to local application of strychnine. *Right*, "Firing" diagram showing interaction between areas. Block triangles: areas strychninized; Y: areas fired; —: areas suppressed (From Bonin, Garol and McCulloch, 1942, p. 188).

SUMMARY

The fact that visual function is dependent upon the integrity of the cortex was first pointed out by Flourens in 1823. Panizza (1855) and Hitzig (1874) were the first to localize visual function in the occipital lobe, and when anatomical studies of the visual projections were made it became obvious that the visual cortex was primarily restricted to the calcarine cortex, or area striata (area 17 of Brodmann).

Neurons from the retina maintain a precise spatial organization in their course from the eye to the external geniculate body, where second-order neurons project, still in precise topographical organization, to the calcarine cortex. Fibres from the nasal half of each retina cross in the optic chiasm, while fibres from the temporal halves of the retina are uncrossed. When the chiasm is compressed in the middle, the crossed fibres are affected and bitemporal defects occur in the field of vision (bitemporal hemianopsia). When the optic tract or optic radiations are

injured, a nasal field defect occurs in one eye and a temporal field defect in the other, leading to a homonymous hemianopsia (half-field blindness). The projections also have anteroventral organization which is the basis of quadrantic defects in the fields of vision.

The posterior occipital poles of man and ape are primarily concerned with macular (central) vision, while the more anterior parts of the calcarine area contain the representation for peripheral vision.

Comparative studies of visual function indicate that the lower animals, such as fish and amphibia, have no essential part of the visual mechanism localized in the forebrain, since removal of the hemispheres produces no impairment of vision. Rabbits and rats have a visual cortex, essential for pattern discrimination, but light discrimination persists after the occipital lobes are completely destroyed. Discrimination of light intensity is also possible in dogs, cats and monkeys after ablation of the occipital lobes. Human beings entirely lose both object vision and light perception when the calcarine cortex is removed.

Areas 18 and 19 are concerned with visual association and their injury causes disturbance in spatial orientation of the visual image of the homonymous half-field; also visual word blindness (alexia).

Area 17 projects to area 18, the parastriate lobule, which in turn projects to the preoccipital area (area 19). Area 19 receives impulses from all parts of the cortex and it thus serves as a centre for coördinating visual with other reflexes.

XVIII

CEREBRAL CORTEX: THE TEMPORAL LOBES

HISTORICAL NOTE

The history of the temporal lobes has been less dramatic than that of the occipital. In 1874 Hitzig recorded that they were inexcitable; in 1876 Flechsig had noted that the medial part of the temporal lobes received numerous fibres from other parts of the cerebral cortex and concluded that it must be an important "association area." Ferrier's (1875) localized ablations quickly followed, Sanger Brown and Schäfer (1888) extending observations to monkeys. Transient visual disturbances were recorded with smell and taste normal, and there were no enduring neurological symptoms except possibly disturbed audition. The auditory radiations had been traced to the superior temporal convolution by Heschl in 1878 and Ferrier (1876) stated that his animals, following bilateral temporal lesions, were deaf, but Brown and Schäfer failed to confirm this in monkeys. In this they were supported by Munk (1881) and by Larionow (1899) who believed that appreciation of musical notes depended on the integrity of the temporal lobes. Kalischer (1910), using trained animals, reached the same conclusion. The belief that the temporal lobes were also concerned with olfactory and gustatory sensation arose from the clinical studies of Hughlings Jackson; in 1889 he and Beevor described "uncinate" seizures, associated with tumours of the medial part of the temporal lobes, in which the patient experienced hallucinations of smell and taste. It was soon recognized, however, that olfactory symptoms were due, not to the temporal lobes, but to involvement of the neighbouring hippocampal gyri (uncus; see ch. xvi). The more recent disclosures concerning the auditory cortex in the temporal lobes will form the principal topic of this chapter.

ANATOMICAL CONSIDERATIONS

THE pathway from the *cochlea* to the cerebral cortex is not a simple projection but involves three, or possibly four orders of neuron (fig. 84; Cajal, 1899). The primary neurons take origin in the cochlea itself, the cell bodies being collected together in Scarpa's ganglion (which corresponds with the dorsal root ganglia of the spinal segments). These primary neurons terminate topically in the dorsolateral part of the medulla oblongata in two cell groups known as the dorsal and ventral cochlear nuclei which give rise to the second order neurons. The projection from the inferior part of the cochlea ends dorsally and that of the superior parts ventrally in these nuclei (Lewy and Kobrak, 1936). The second order neurons terminate variously in the trapezoid body, olives, pons,

inferior colliculi, and it is believed that few of the second order neurons actually pass to the medial geniculate body (Lorente de Nó, 1933, 1935a). The third order neurons arise in the various way-stations just mentioned and project directly to the medial geniculate body. In the diagram (fig. 84) no evidence of ipsilateral thalamic projections is indicated. Anatomically such fibres have not been established, but their existence has been postulated on physiological grounds. The fourth order neurons take origin solely from the medial geniculate body (ch.xv), and they all project to the auditory koniocortex lying in the anterior wall of the Sylvian fissure in the middle part of its extent. For the actual determination of the area of auditory projections we are indebted to Mettler (1932) (cat), Polyak (1932) (monkey), Le Gros Clark (1936), and to the more recent work of Walker (1938) who has given a sharp delimitation of this area in both macaque and chimpanzee.

All impulses from the auditory mechanism not concerned in brain stem reflexes must therefore pass through the medial geniculate body, and they all reach the cortex in a relatively restricted focus. The organization of the projections from the point of view of spatial relations in the cochlea is not yet determined, but one may presuppose a point-to-point projection similar to that occurring in the visual system though less precise (Pennington, 1937). Further details concerning the relations of auditory fibres in the eighth nerve and their extraordinarily complex arrangement in the cochlear nucleus will be found in the monograph by Stevens and Davis (1938).

The *vestibular* projections take a similar course from the vestibular nuclei with a corresponding number of synaptic interruptions, but the anatomical details of this projection are more obscure; their relation to the thalamus is imperfectly worked out (probably medial geniculate).

The vestibular projections of the forebrain have been studied by several investigators. Held (1897) traced a tract from the vestibular nuclei to the reticular substance and to the lateral part of the ventral nuclei of the thalamus. Whitaker and Alexander (1932) found after experimental injury of the vestibular nuclei (dog) Marchi degeneration in the posterior longitudinal fasciculus extending to the red nucleus, the hypothalamic nuclei (paraventricularis) and also some degeneration to the nucleus proprius of Meynert. Recently Godlewski (1936) has recorded similar findings tracing degeneration to the hypothalamus and to the reticular substance, centromedian and the medial nuclei of the thalamus. The cytoarchitectural areas to which the vestibular thalamocortical fibres project have not yet been determined, although Spiegel's (1934) work would suggest that it lies just medial to the auditory cortex

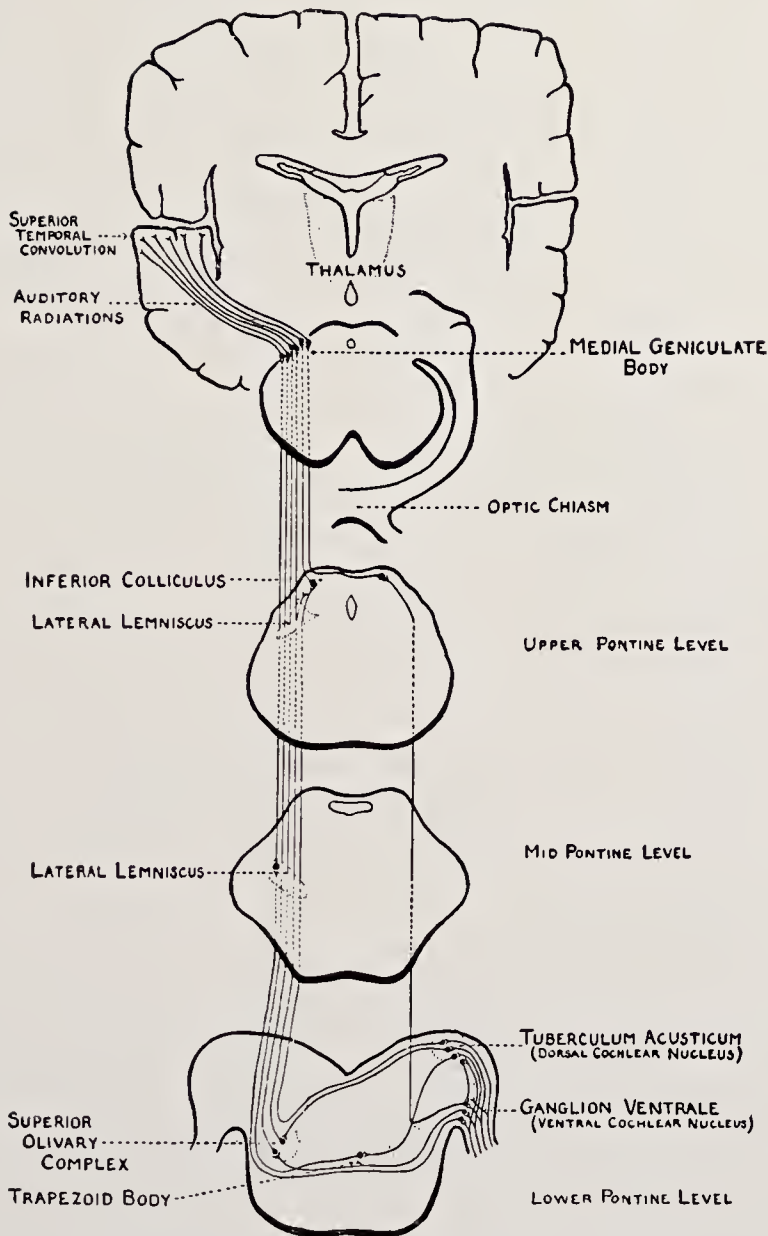


FIG. 84. Diagram of principal auditory pathways. Successive transverse sections are indicated to various levels of the brain stem with vertical section through cerebral hemispheres at level of Heschl's convolution. Neurons of auditory nerve are indicated with one pathway for each type (Davis, from *A handbook of general experimental psychology*, Clark University Press, p. 967).

EXPERIMENTAL STUDIES ON ANIMALS

The temporal lobes thus receive fibres from the auditory, vestibular and also from many intracortical systems, but despite this variety of afferent connections the physiology of the temporal lobes is imperfectly known, and, like the frontal association areas, they have until recently been regarded as virtually "silent areas." Some light has been thrown upon them through experimental study, but the more important observations have been made in clinical cases (Börnstein, 1930; Pfeifer, 1936). As indicated in the historical note, the temporal lobes have been ablated from untrained animals without causing significant symptoms. More recent studies, involving both ablation and stimulation, have thrown some light upon the auditory and vestibular functions of this region.

AUDITORY FUNCTIONS. Walker's (1938) delimitation of the site of termination of the auditory projections from the medial geniculate bodies upon a restricted part of Heschl's convolution gives welcome support to the old belief that this area is concerned with audition. Faradic stimulation of this part of the superior temporal convolution in conscious human patients is without conspicuous motor effect, but it has given rise to subjective auditory sensation — buzzing, clicking, booming, etc. Such reactions have been reported by Foerster (1936), Pfeifer (1936) and others; animals are said to "prick up" their ears when this region is faradized (Schäfer, 1900).

Davis' (1934) action current studies upon various parts of the auditory system have indicated that the spontaneous action current rhythms from area 22 in cats are markedly altered by loud sounds (especially clicks). Within certain limits the action current rhythm corresponds for low tones with the tone itself. Such electrical rhythms can be obtained from the auditory area and from no other part of the cerebral cortex. More recently Galambos and Davis (1943a&b) have isolated single nerve fibres when responding to sounds of different frequency and intensity. They find furthermore that a tone of one intensity may inhibit another tone and thus account for the phenomenon of tone masking. To quote their latest report (1943b):

"For each single auditory-nerve fiber (cat) there is a 'response area' clearly defined in terms of the frequency and intensity of the tones which excite activity. For most fibers the discharge of nerve impulses aroused by such adequate tones

(T_1) can be reduced or abolished by other tones (T_2) or by noises (hiss or rattle) presented concurrently. Not all tones inhibit the response to T_1 . Those which do inhibit fall into one or more well-defined "inhibitory areas" which are different for different fibers and for different T_1 s presented to a given fiber. The inhibitory areas are adjacent to the response areas and often include some tones which lie within the response area. For a few fibers no single pure tone (T) inhibits the response to T_1 , but in such cases the activity can usually still be abolished by noises.

"Inhibition of auditory-nerve activity by acoustic stimulation might result from mechanical interference in the auditory receptor or from neural interaction. Control experiments seem to exclude mechanical interference at the middle ear or basilar membrane level as an explanation."

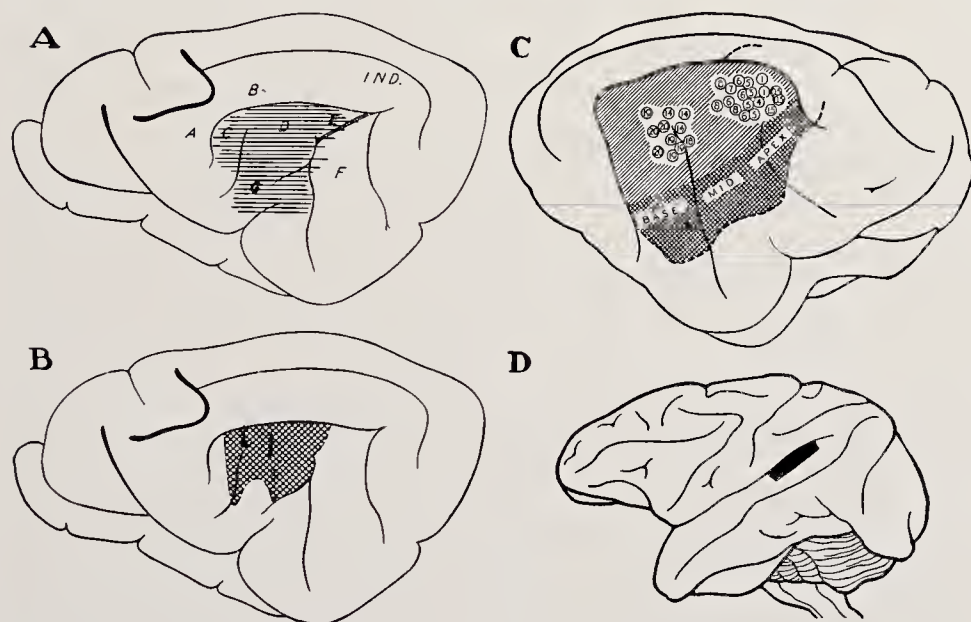


FIG. 85. Diagrams of acoustic cortex in cat and monkey. A, Bremer and Dow's (1939) indication of area from which electrical responses were evoked to clicks. B, Cytoarchitectonic limits of koniocortex from one of Bremer and Dow's experiments. C, Woolsey and Walzl's (1942) delimitation of the acoustic cortex of cats responding to isolated stimulation of specific points on the cochlea, the base (low notes) being projected to the rostral acoustic area, the apex (high notes) to the caudal. Cross hatched region indicates secondary acoustic area activated by more intense stimulation. In the secondary acoustic area the distribution of foci from the cochlea is laid down in the reverse of that for the primary area. D, Ades and Felder's (1942) representation of the acoustic area of monkeys.

The physiology of audition has been notably advanced during the past five years. Identification of the acoustic cortex of cats was clearly established by Bremer and Dow (1939) through recording cortical electrograms induced by abrupt sounds (clicks). The area of responsiveness on the upper part of the sylvian gyrus (fig. 85A) corresponds with a cytoarchitecturally discrete area (fig. 85B). Woolsey and Walzl (1942)

through isolated stimulation of various turns of the cochlea have demonstrated a point-to-point projection from cochlea to cortex, in which the base of the cochlea (low notes) projects rostrally and the apex (high notes) caudally on the acoustic area (fig. 85c).^{*} Ades and Felder (1942), employing a technique similar to that of Dow and Bremer, have identified the acoustic area of the monkey (fig. 85p), and Licklider and Kryter (1942) have established that lower frequencies produced their maximal effects in the antrolateral part of area 22 and higher frequencies in the posteromedial area, the representation thus of the cochlea having the same regional distribution as in the cat. Similar tonotopic localization within the primary auditory cortex has been established by McCulloch, *et al.* (1942), for the chimpanzee.

In addition to the primary auditory cortex, Woolsey and Walzl (1942) and Ades (1943) recognize a *secondary acoustic area* with well-defined connections in the medial geniculate body (pars magnocellularis). The secondary area tends to respond to more intense stimulation and involves a region cytoarchitecturally distinct from the primary acoustic area. A similar secondary acoustic area has also been recognized in the monkey, and it no doubt plays a part in the integration of acoustic reflexes similar to that played by areas 18 and 19 for visual reflexes. Woolsey and Walzl conclude that "since the fibres of the cochlear nerve are distributed in an orderly manner to the organ of Corti, localized regions of which respond optimally to particular frequencies of the sound spectrum, demonstration of a 'point-to-point' projection of these fibers to the cerebral cortex provides an anatomical basis for tonal localization in the cerebral mantle."

Ablation studies have given less definite results. Following symmetrical bilateral ablation of the temporal lobes in a trained baboon, the animal was essentially normal in its behaviour and reacted normally in the delayed reaction test (Jacobsen and Elder, 1936). There was a slight upper-quadrant visual defect. The animal poorly localized the direction from which the sounds came, *but it was not deaf*, and there was no suggestion that it failed to recognize the significance of sounds such as the spoken command. Wendt, in a well controlled study involving monkeys and baboons trained for the determination of auditory activity (1934) found slight impairment of acuity after subtotal ablation of the auditory cortex (Wendt, unpublished).

^{*} One difficulty in working out the projection of the cochlea on the cortex was that single tones presumably activate a wide stretch of basilar membrane and hence a wide band of cortical projection fibres. Woolsey and Walzl (1942) developed an ingenious technique for tearing away the basilar membrane and stimulating a few nerve fibres as they enter the modiolus, and obtained narrow bands of electrical activity in the auditory cortex.

Culler and his collaborators(1936)made an ingenious analysis of the components of the auditory system of cats from which they drew the following conclusions: "Destruction of one cochlea, in a cat otherwise intact, is followed by a hearing loss of 3 to 4 decibels. Destruction of both cochleae eventuates in total deafness to air-borne sounds(no response to tones 125 decibels above the animal's normal threshold). Ablation of a single half of the cortex is followed by a hearing loss of the same magnitude — 3 to 5 decibels. Statistical analysis indicates that the left hemisphere may be slightly superior in acoustic value to the right; but in any event there is no substantial disparity. In cats with one half of the cortex ablated, destruction of the heterolateral cochlea causes an additional drop in acuity, owing to exclusion of the *crossed* fibers of the lateral lemniscus, of 15 decibels. In cats with one half of the cortex ablated, destruction of the homolateral cochlea causes an additional drop in acuity, owing to exclusion of the *uncrossed* fibers of the lateral lemniscus[see Lewy and Kobrak, 1936], of 13 to 14 decibels. It follows that the uncrossed fibers of the auditory system are virtually equal in acoustic significance to the crossed components. Statistical analysis fails to reveal even a presumptive superiority of the crossed pathways. The evidence discloses a satisfactory safety-factor in the acoustic system, which compares favorably with that found in other physiological systems and with good engineering practise. By use of testing-equipment recently developed in this laboratory, it was made feasible to institute a systematic program of quantitative hearing-tests in post-operative cats. The above conclusions confirm and considerably extend conclusions previously derived in this laboratory from dogs"(Brogden, *et al.*, 1936).

Wiley(1932)and Pennington(1935)have studied the auditory cortex of rats which had been trained to react to certain sounds. Although the animals can re-acquire auditory habits after bilateral ablation of the temporal lobes, Pennington's latest work(1937a&b)indicates that such ablations, corresponding anatomically with the area of the auditory projections, abolishes auditory habits, especially those based on localization of sound; no other cortical ablation has this effect.

Finally, Klüver and Bucy(1938)have described a syndrome of "psychic blindness," following an extensive bilateral ablation of the temporal lobes which may conceivably have involved area 19. Monkeys are terrified of snakes; after bilateral ablation of the temporal lobes, the animals handled snakes freely and showed no reactions of fear in the presence of objects which they had previously been trained to dread. Furthermore, the animals seemed totally unable to recognize objects by sight(or touch). When a series of 8 or 10 different objects were placed before an intact animal, it would pick up the edible articles and ignore the rest. The animal from which both temporal lobes had been removed would pick up the various articles at random — even to trying a chalk mark — would carry them to its mouth, and only then discard those that were inedible.

VESTIBULAR FUNCTIONS. Subjective dizziness also occurs when certain parts of the temporal lobes are stimulated faradically in conscious human subjects, the symptom being also common in expanding tumours of this region. Spiegel(1934)has offered suggestive evidence that vestibular impulses reach the temporal lobes in dogs and cats. After painting a suspected area with strychnine, one obtains convulsive movements when the sensory end organ projecting to the area is stimulated. After

strychninizing the temporal gyri, Spiegel stimulated the labyrinth by simple rotation or by "caloric" stimulation(ch. xi). Convulsive movements were immediately induced. These he interpreted as due to the spread of vestibulotemporal excitation to the motor regions of the cortex. These studies were further substantiated by leading off action currents from the strychninized area, the action current rhythms increasing conspicuously during stimulation of the vestibular nerve. Aronson(1933), working with Spiegel, found, after section of the VIIIth nerve, that rotation of animals with strychninized temporal lobes failed to produce convulsions. However, following ablation of the temporal lobes no disturbances in equilibrium or diminution in reaction to vestibular stimulation are known to occur.

CLINICAL STUDIES

Clinical investigations of the temporal lobes are less disappointing than purely physiological work, but there is much still to be derived from both sources. A syndrome of temporal lobe deficit is now widely recognized(Horrax, 1923). The earlier observations were based on analyses of the symptoms produced by temporal lobe tumours; the more recent studies have been made on human beings from which the temporal lobe has been surgically removed(Frazier and Rowe, 1934; Fox and German, 1935).

Dominance of left cerebral hemisphere in man. In approaching the functions of the human brain there is one conspicuous phenomenon which distinguishes it from the brains of lower animals, namely, the tendency for certain functions to be concentrated in the left cerebral hemisphere of right-handed individuals; the phenomenon is generally referred to as "left cerebral dominance." Thus a lesion of the third frontal convolution of the right hemisphere in a right-handed man causes no recognizable disturbance, whereas lesions of the same area in the left hemisphere give rise to grave motor "aphasia"(ch. xxii). In studying the functions of the temporal lobe, one encounters the same phenomenon, for with lesions of the right temporal lobe in right-handed individuals disturbances of speech are not encountered, whereas with similar lesions of the left temporal lobe the speech mechanism is generally affected.

The basis of this feature of organization in the human brain has been much discussed, especially in treatises on speech disturbances(Orton, 1937). There is no doubt that it is associated with "handedness," and that attempts arbitrarily to alter a natural dominance, such as trying to make a left-handed child right-handed, often causes grave intellectual disturbances, including aberrations of the speech mechanism. The ultimate implications of left cerebral dominance are, however, more a matter for the psychologist and the practising neurologist to consider than the neurophysiologist, who has little to offer in the way of relevant discussion.

The earliest recognized symptom of temporal lobe tumours was the so-called "uncinate fit," which was reported by Hughlings Jackson and Beever in 1889. As pointed out in the historical note to the last chapter, the symptom itself is not due to the temporal lobe at all but to encroachment upon the adjacent structures in the rhinencephalon, principally the uncus. The incidence of uncinate fits is actually rather low (Frazier and Rowe, 1934), and they evidently occur only with the more medially situated tumours. The other symptoms associated with lesions or ablations of the temporal lobes are as follows:

Auditory symptoms. In Frazier and Rowe's series of fifty-nine verified tumours of the temporal lobe, auditory disturbances were the most frequent sign of temporal lobe involvement. They took the form of tinnitus, moderate diminution of auditory activity restricted to the period of the patient's illness, and generally the symptoms were bilaterally referred, although there were three instances of unilateral and one of contralateral tinnitus. Relative deafness, however, was generally unilateral. There was one case of auditory hallucination in which the patient heard voices. Ablation of the auditory cortex clearly does not cause deafness in animals or man, but when left-sided it may cause disorganization in which the patient hears the sounds but fails to associate the usual meanings with them. This may involve failure to appreciate the meaning of sound, or it may even extend to the loss of meaning of specific words — verbal aphasia.

Penfield and Gage(1934) have described epileptic seizures originating from foci in the superior temporal convolution. In one case, the attack began with an aura of buzzing and ringing in the ears, followed by a sense of dizziness, "head swimming," etc. In another case having a somewhat similar attack, stimulation of the cortex in the region of the lesion caused a dizzy feeling, and a "buzzing" sound similar to that which preceded each attack. Sounds may precipitate an attack. As yet no one has had an opportunity to study a bilateral temporal lesion in man, nor have the effects on hearing from bilateral lesions been investigated adequately in animals. Since auditory representation is probably bilateral, it is likely that cortical deafness would not occur unless both auditory areas were injured. See also Penfield and Erickson(1941).

Visual disturbances. The visual radiations from the lateral geniculate body to the calcarine cortex sweep around the lateral horn of the cerebral ventricle in the white matter of the temporal lobe(ch. xvii; fig. 79).

Cushing(1922)in his series of 59 verified temporal tumours found that 39 of them exhibited defects in the visual field in the upper homonymous quadrant opposite to the lesion, indicating that the visual radiations for peripheral vision had been affected. Generally the macular representation is not spared. Visual hallucinations are also frequently described in temporal lobe tumours, especially those situated somewhat posteriorly which implicate area 19, and are typically formed hallucinations.

Speech. With left-sided temporal lesions in right-handed individuals some degree of speech disturbance generally develops. Auditory receptive mechanism is deficient, and particularly conspicuous is a deficiency in auditory speech and memory. Fox and German's cases, however, appear to be particularly cogent and in line with what one would anticipate from a cortical disturbance of the auditory projection.

"Dreamy states." Hughlings Jackson(1931)and Foster Kennedy (1911), in analyzing temporal lobe symptomatology, drew attention to states of arrested consciousness akin to epileptiform seizures, but unaccompanied by convulsions. Olfactory hallucinations are sometimes present. The patient suddenly passes off into a dream world and sometimes has vivid hallucinations with auditory or visual components, often recovering within a few minutes. Although of frequent occurrence, exact significance of the dreamy state has not been ascertained; such states, however, are often prodromal, in the case histories of such tumours, to more severe seizures accompanied by motor convulsions. Gibbs(1932) found that 33 per cent of generalized convulsions in 1545 cases of brain tumour were with tumours of the temporal lobes.

SUMMARY

The temporal lobes receive auditory projections from the medial geniculate body, and the vestibular projections from sources as yet undetermined.

Stimulation of the region of the auditory projections causes auditory sensations of buzzing and roaring in conscious human subjects, while giddiness and a sense of falling is evoked from closely adjacent regions. Auditory and labyrinthine stimulation causes a marked increase in the electrical reactions of area 22, and of no other part of the cerebral cortex.

Since the fibres of the cochlear nerve are distributed in an orderly manner to the organ of Corti, localized regions of which respond optimally to particular frequencies of the sound spectrum, demonstration

of a "point-to-point" projection of these fibres to the cerebral cortex provides an anatomical basis for tonal localization in the cerebral mantle.

Ablation of the temporal lobes does not cause complete deafness, but there is change in auditory acuity (Wendt's trained monkeys); in man there is some deafness and contralateral disturbance of auditory localization (direction of sound) as well as in memory for auditory impressions. Bilateral ablation of the temporal lobes does not produce deafness in animals, but probably causes disturbance in appreciation of the significance of sounds and — in man — of spoken language.

Strychninization of the temporal lobes, and of no other part of the brain, causes labyrinthine stimulation to bring on convulsions, due to hyperactivity of vestibular reflexes involving the cortex. Section of the VIIIth nerve abolishes the phenomenon.

Clinical symptoms of temporal lobe tumours include visual field defects (from encroachment upon the optic radiations), auditory disturbances, speech defects, and, in the early stages, minor seizures referred to as "dreamy states." With medial tumours, seizures may implicate the uncus, and in these circumstances give rise to hallucinations of smell and taste (uncinate seizures).

XIX

CEREBRAL CORTEX: THE PARIETAL LOBES AND SOMATIC SENSATION *

HISTORICAL NOTE

The studies of Hughlings Jackson on the frontal lobes (ch. xxi) led him to recognize that clinical lesions situated near the central sulcus were prone to cause disturbances in the sensory sphere. In 1863 Jackson described a case of sensory epilepsy referred to the thumb, and in the next thirty years, during which much of his attention was devoted to cerebral seizures, he laid more and more emphasis upon the importance of their sensory manifestations. In 1887, he wrote: "I have long held the hypothesis that the whole anterior lobe is (chiefly) motor" . . . and "that the posterior part of the brain is (chiefly) sensory." He thus appreciated that overlapping occurred in sensorimotor representation, but he stoutly maintained, long before adequate physiological evidence was available, that the parietal lobes were primarily sensory in function. Although the problem of sensory representation in the cerebral hemispheres was actively investigated by physiologists, it was not until the beginning of this century that the parietal lobes were conceded by all to be the locus of sensory cortical processes. English investigators, Ferrier (1873), Horsley and Schäfer (1888) and Schäfer (1898) (see also Mott, 1894), insisted that tactile sensibility was localized in the cingular or hippocampal gyri. The Continental investigators (Hitzig, Schiff, Munk, Nothnagel, Bechterew) from the first favoured localization on the convexity of the brain in front, as well as behind, the central fissure (Dana, 1888). The sensory area was then coextensive with the electrically excitable or motor area, which until the work of Grünbaum and Sherrington (cf. ch. xx) was believed to extend well into the parietal lobes. In fact, Schiff, Munk and others held that the motor responses to stimulation and the paralytic effect of ablation of the precentral gyrus were actually sensory in origin. The significance of the central fissure as a functional boundary being unappreciated, the pre- and postcentral regions, except in a few experiments of Bechterew, were apparently never separately ablated. It is clear, therefore, that the "unitarian" or "sensorimotor" view, at least in its inception, was philosophic in origin and entirely without an experimental basis. With the proof that the central fissure is the posterior boundary of the motor region came the view — again without adequate experimental basis — that the central fissure is the forward boundary of the sensory area. It is not improbable that the pendulum has swung too far, since there is growing evidence, anatomical and physiological, that the precentral gyri are concerned with sensory functions.

The character of cortical sensory processes, as well as their topographical details of localization, have dominated the investigation of the parietal lobes in the present century. The pioneering work on the first of these problems was that of Munk (1881). To understand cortical sensory defects, it is necessary, he argues, to distinguish between sensibility to light touch, or pressure (*Sinnesempfindung*),

* The present chapter has been largely written and revised by Dr. T. C. Ruch, to whom I am much indebted. — J. F. F.

manifested in delicate isolated movements and dependent upon the cerebral cortex; and generalized motor responses to strong stimulation (*Gemeinempfindung*), presumably unconscious and elicitable after complete ablation of the cortical sensory areas. An example of Munk's "cortical reflexes" is his *Berührungsreflexe*, a delicate plantar flexion of the foot to light stroking of the dorsum. Similar cortical reflexes of Rademaker (1931) have been recently studied by Bard and his co-workers after lesions of the cortex in cats and monkeys (ch. x). The classical papers of Head and Holmes (1911) and Head's (1918) record of war cases in which psychological concepts, as well as psychological testing methods, were employed were the first comprehensive investigations to be concerned with the *nature* rather than the *locus* of cortical sensory processes in man. They demonstrated that cortical lesions produced, not anesthesia, but a selective disruption of the discriminative and integrative functions underlying perception. Ablation experiments upon animals have been few and have contributed comparatively little, presumably because sensory disturbances cannot be adequately interpreted from gross clinical examination. That of Minkowski (1917) is the single extensive study in which isolated regional ablations of the pre- and postcentral convolutions in the monkey were attempted and the defects carefully observed over a long postoperative period. Although a model of its kind, it served to emphasize the need for more objective methods of studying sensation in animals.

CLINICAL and physiological studies of the parietal lobe have until recently been handicapped by inadequate knowledge of the anatomical substrate. The illuminating analysis of thalamocortical projection by Polyak, Le Gros Clark and Walker provides a concrete basis for the design and interpretation of physiological studies. Prior to Polyak's work (1932), and despite much affirmative evidence (Déjerine, von Monakow, Probst, Vogt, etc.), the fact that part of the thalamocortical projection actually passes to the precentral convolution (ch. xiv) was largely neglected. Similarly, Flechsig's designation of the parietal lobe as a "primary sensory area," into which all somatic sensory impulses pour and from which they are transmitted to the parietal association area for elaboration, can no longer be sustained. The "association area" being in receipt of a projection from the thalamus is also a projection area. If the sensory area in its broadest meaning is defined as that area of the cortex which receives a projection from thalamic nuclei which are connected with the great ascending sensory systems, then it spreads over a large area of the frontal lobe and the whole of the parietal lobe; the prefrontal area cannot be excluded on *à priori* grounds. This area is not homogeneous throughout either in cytoarchitecture or in the character of its projection (see ch. xiv), and at least three subregions should be distinguished as indicated in the table on the next page.

One of these subregions, the postcentral gyrus, receives a topographi-

FUNCTIONAL DESIGNATION	MORPHOLOGICAL DESIGNATION	CYTOARCHITECTURE	TYPE OF PROJECTION
Primary sensory area	Postcentral convolution	Areas 3-1-2	Connected through posteroventral nuclei with mesial and trigeminal fillets and spinothalamic tract.
Parietal association area	Posterior parietal lobe or lobule	Areas 5 & 7	Connections through posterolateral nucleus via intrathalamic fibres with posteroventral nuclei and ascending systems.
Motor and premotor areas	Precentral convolution	Areas 4 & 6	Connected via the lateroventral nucleus and the superior cerebellar peduncle with the spinocerebellar afferents.
Frontal association area	Prefrontal area or frontal pole	Areas 9-10-11-12	Projections from the dorsomedial nucleus which has unknown intrathalamic connections.

cally highly organized projection. This means that the body surface is projected upon the cortex with the spatial relation dermatome to dermatome maintained intact, a neural pattern which certainly must be involved in the localization of touches on the skin and other perceptual processes having a spatial element. Physiological evidence of this projection of the body surface upon the cerebral cortex has come from electrical stimulation of the parietal lobe in man, by strychnine stimulation in monkeys, and, quite recently, from mapping the loci of electrical activity of the cortex when different areas of the body surface are stimulated.

EXCITATION OF PARIETAL LOBES

ELECTRICAL STIMULATION. The cerebral cortex of man was stimulated in 1874 by Bartholow, who recorded odd sensations referred to the legs when an electrical stimulus was applied to the exposed cortex in a patient whose postcentral convolution presented through a wound of the skull. A similar case was recorded by Ransom in 1892. No systematic observations of this character, however, were made until 1909 when Cushing recorded the effects of parietal lobe stimulation in a conscious human being whose cerebral cortex had been exposed under local anes-

thesia. He found that stimulation of the superior part of the postcentral convolution gave rise to sensations referred to the lower extremity, the middle part to sensations referred to the trunk and upper extremity, and the lower part to well defined sensations in the face. Obviously this distribution coincides closely with the distribution of excitable points in area 4; it coincides, moreover, with the spatial organization of thalamo-cortical projections from the posteroventral nuclei of the thalamus. The subjective sensations evoked by stimulation of the postcentral convolution consisted in tactile and pressure hallucinations, *i.e.*, sense of constriction referred to the wrist and fingers, and occasionally thermal sensations were reported by the patient, although never pain. The character of the localized sensory phenomena such as those reported by Cushing has been confirmed by Foerster(1936b), van Valkenburg(1914, 1916), and more recently in an extended series of observations by Penfield and Boldrey(1937). From the latter's map showing the distribution of points from which sensations were elicited(fig. 86), it will be seen that *stimulation of the precentral gyrus, particularly along its posterior lip, gives rise to sensations*. These were similar in quality to those resulting from excitation of the postcentral gyrus and their occurrence is in accord with the existence of a thalamic projection to this area. Zonal representation of specific sense modalities was not observed. Sensations of pain, warmth and cold were rarely reported, the most common responses being numbness, tingling and a sense of movement unaccompanied by actual movement. According to Foerster, areas 5 and 7 also yield sensory responses if the stimulation is intense. In the more lateral parts of area 7, auditory and visual hallucinations may be evoked, but the latter are more intense when area 19 is stimulated.

LOCAL STRYCHNINIZATION OF CEREBRAL CORTEX. Many obstacles encountered in the study of sensory phenomena of the cortex arise from the inevitable difficulty of interpreting responses of animals to impaired or absent sensory modalities. The method of Dusser de Barenne(1916) of inducing positive sensory phenomena — hyperesthesia, paresthesia and hyperalgesia — through local application of strychnine has given a new and wholly objective procedure for analyzing sensory localization in the cortex. These sensory impressions though originating in the cortex itself are, like the sensations from a phantom limb, referred to the body surfaces, and the animal responds by scratching, biting, or otherwise indicating the area of skin to which the sensations are projected.

On application of strychnine to a few square millimetres of parietal cortex, sensory disturbances develop on both sides of the body. They are strongest on the contralateral side, but present also ipsilaterally. Disturbance of certain phases of deep sensibility, *i.e.*, hypersensitivity to pressure on muscles, periosteum, etc., can generally be demonstrated only on the

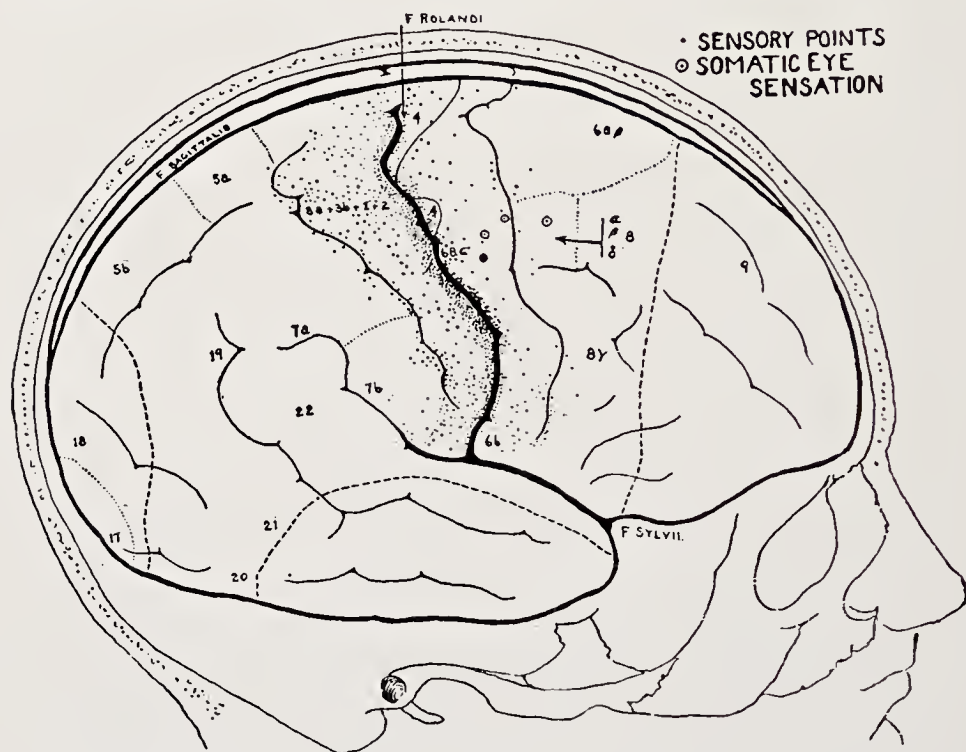


FIG. 86. Distribution of points on cerebral cortex at which stimulation evoked sensation in conscious human patients(after Penfield and Boldrey, 1937).

opposite side(cf. ch. xv), but the cutaneous surface gives evidence of hyperesthesia, paresthesia, and sometimes hyperalgesia on both sides.

Study of the effects of strychninization has led to a separation of the sensory cortex into three major divisions corresponding with area 4, namely,(i) a leg area,(ii) an arm and trunk area,(iii) a face area; the boundaries between these subdivisions are precise and respected even by strychnine(which generally causes diffuse discharge when introduced into the central nervous system). Irradiation from leg to arm has never been observed on local application of strychnine to any one of these primary subdivisions of the postcentral convolution. An explanation of this is given later in this chapter.

The area which gives rise to sensory symptoms is rather extensive. The posterior boundary coincides with that of the parietal lobe. Moreover, the area extends in front of the central fissure and includes the whole agranular frontal cortex (areas 4 and 6). Within the precentral area the same topographical subdivisions exist; indeed, no difference in symptomatology could be detected from pre- and postcentral strychninization. This sensory area, as demarcated by strychnine stimulation, then agrees with that established by the study of thalamocortical projections. Dusser de Barenne's evidence, though dependent on an abnormal form of stimulation, clearly establishes some sort of participation of the precentral convolution in cortical sensory processes and is strong affirmative evidence that the sensory area overlaps the motor representation. The evidence does not entirely harmonize with ablation studies of areas 4 and 6, particularly in respect of cutaneous sensation, but, as Dusser de Barenne (1935) points out, "This similarity in the symptomatology on strychninization of the pre- and postcentral cortex can only be interpreted as demonstrating that strychnine, in bringing about the maximum of sensory functions, blurs finer functional differentiation."

It is not surprising that experiments employing strychnine, a powerful stimulus giving positive sensory symptoms, should not agree exactly with ablation experiments depending upon negative symptoms. Moreover, the wide extent of the sensory cortex demarcated by strychnine stimulation may prove to be the explanation for the compensation of defects from parietal cortical lesions in monkeys. It might be thought that the sensory symptoms which result from strychninization of areas 4 and 6 are mediated through the parietal lobes just as the electrical excitability of the postcentral gyrus has been shown largely to be mediated through the motor area. That such is not the case is shown by the following experiment by Dusser de Barenne: In a monkey the whole of the arm area (strychnine stimulation) of both hemispheres was destroyed except for that lying in the precentral gyrus of one cortex. Strychninization of this remaining island of sensory cortex in the precentral gyrus continued to give rise to sensory symptoms. Parallel observations on strychnine stimulation of the cortex of chimpanzee and of man would be of value.

That strychninization of a few millimetres of the sensory arm area causes symptoms over the whole of the arm is believed to indicate, not that the whole arm is re-represented in each unit area but that the small area of activated cortex serves to "fire off" the whole arm representation in the sensory cortex and in the corresponding thalamic nucleus. This is entirely consistent with the fact that injection of strychnine into thalamic nuclei gave similar symptomatology. All the evidence points to some type of interaction between the sensory cortical areas, including areas

4 and 6, and the thalamus. Further evidence favouring this interpretation has come from the more recent investigations of Dusser de Barenne (1937), in which the electrical responses of the postcentral convolution, as well as those of the thalamus, have been studied in response to local application of strychnine to the precentral convolution and postcentral region respectively.

Electrical reaction to strychninization. When the postcentral leg area is strychninized at a small focus, the whole leg area begins at once to show a succession of large action current "spikes," indicating that many neurons of the region are in simultaneous activity. Dusser de Barenne refers to this reaction picturesquely as "setting the cortex on fire." When area 2 for the leg is "fired" in this manner, the activity spreads to the precentral leg area; but, curiously enough, strychnine on area 1 (leg) inhibits the action currents of area 4a. The activity from the sensory leg area never spreads to the sensory arm area or the motor arm region. However, when area 6a β is activated, the sensory arm area and sensory leg area are both "fired," and even the face area may show a conspicuous increase in electrical activity. This is in harmony with the fact that faradic stimulation of area 6a β (ch. xxi) may cause activity of the entire contralateral musculature (Dusser de Barenne and McCulloch, 1938b). A similar functional mosaic, though more intricate, has recently been found by Bailey, *et al.* (1940) to characterize the humanoid cortex of the chimpanzee. An important result of these studies is that they provide fresh evidence that the parietal and frontal sensory areas are functionally interrelated.

Owing to the corticothalamic projections, strychninization of either pre- or postcentral convolution also causes "firing" of the thalamic nuclei.

ACTIVATION OF THALAMUS BY STRYCHNINIZATION OF CORTEX. Dusser de Barenne (1937) has found that local strychninization of either the postcentral or precentral leg area causes conspicuous augmentation of electrical activity in the lateral part of the thalamic nuclear mass. Strychninization of the arm area, frontal or parietal, similarly activates the more medial part of the lateral nuclear mass (n. ventralis posterolateralis), and from the sensory face area and areas 4c and 6a (lower part) there is activation of the region corresponding with n. ventralis postero-medialis. Dusser de Barenne has not been able, by the electrical method, to distinguish between the lateroventral and posteroventral nuclei. His

observations clearly indicate that the corticothalamic projections must have a precise organization. He was not able, on the basis of his studies, to distinguish between the post- and the precentral projections from the point of view of thalamic activation. Since strychnine applied to area 6 activates both areas 4 and 3-1-2, it is possible that thalamic activation from the precentral region *in part* occurs via the postcentral convolution (Spiegel, 1937). While strychninization of the cortex of one hemisphere induces bilateral symptomatology, it activates only the thalamic nuclei of the same side; unilateral strychninization of the thalamus has also a bilateral effect. All this is quite in accord with anatomical data showing that there is no crossing of fibres from one half of the thalamus to the contralateral cortex, but that each half of the thalamus receives cutaneous sensory impulses from both halves of the body.

ELECTRICAL REACTIONS TO PERIPHERAL STIMULATION

The clinical literature contains evidence that lesions of the parietal lobes may give rise to sensory defects having a dermatomal distribution. From electrical and strychnine stimulation one gains a more precise knowledge of the topographical organization of sensory representation, especially in areas 3-1-2. Evidence of a still more detailed projection of the body surface upon the postcentral gyrus was recently gained through the important work of Woolsey, Marshall and Bard (1942) by correlating the area of skin stimulated with the site of electrical activity on the postcentral cortex. Whereas previous methods allowed mapping of the sensory cortex into leg, arm and face areas — a regional projection — these workers have demonstrated a dermatomal organization. Bard (1941) states that within areas 3-1-2 of Brodmann "the parts of the contralateral body surface are represented in an orderly sequence. In the case of the lower extremity this sequence clearly reflects the metameric origin of the dermatomes; the arrangement is in the order of spinal innervation, not in the order — hip, thigh, knee, leg, ankle, foot, toes."

In the ladder-like representation of the body surface shown in figure 87 there is an interesting departure from the dermatomal order of spinal innervation. Though the representation of the arms follows the dermatomal order it is reversed end-for-end so that the most caudal dermatomes of the arms are projected adjacent to the upper margin of the face area, which is the representation of the chin. This discovery undoubtedly accounts for some of the puzzling features of the march of

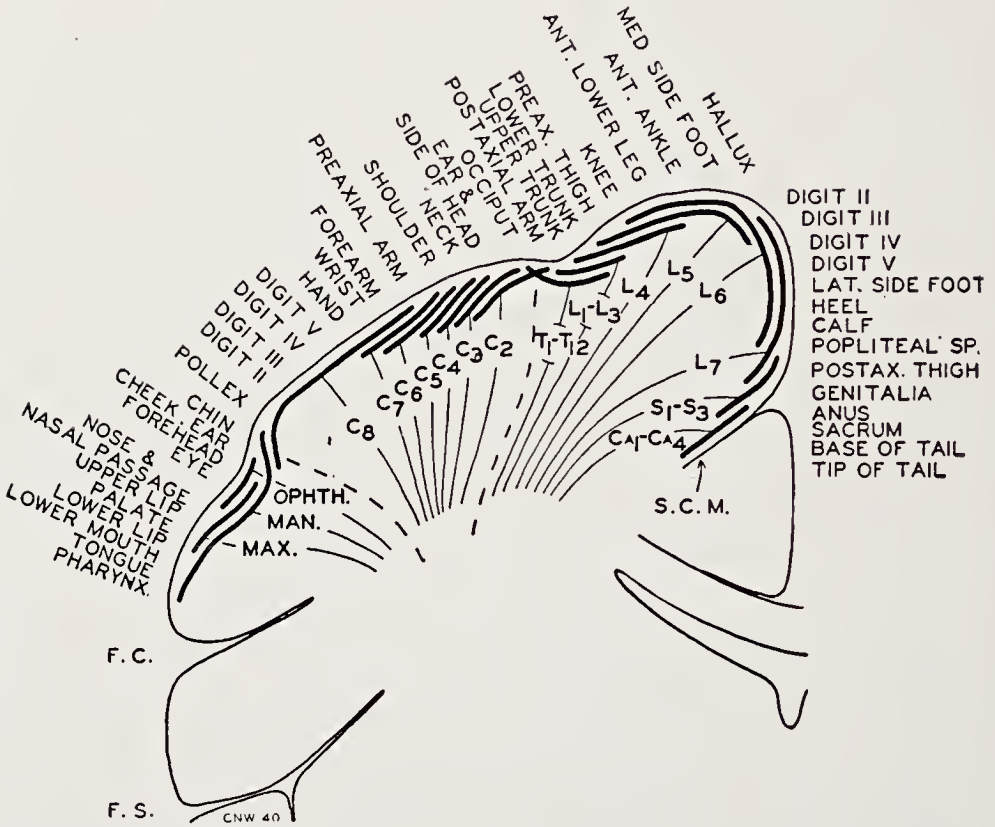


FIG. 87. Schematic frontal section through postcentral gyrus of monkey illustrating the dermatomal projection and overlap of successive dermatomes of the parietal lobe. Note that whereas the sacral, lumbar and thoracic dermatomes proceed in orderly sequence, the order of the cervical dermatomes is reversed. F.S., Sylvian fissure; F.C., central fissure; S.C.M., callosomarginal sulcus; MAX., maxillary; MAN., mandibular; OPTH., ophthalmic; C., cervical; T., thoracic; L., lumbar; S., sacral; Ca., caudal. (From Woolsey, Marshall and Bard, *Johns Hopk. Hosp. Bull.*, 1942, 70, p. 428.)

sensory epilepsy and the distribution of sensory defects from small cortical lesions. In this also lies the explanation of the puzzling hair-line boundaries in the strychnine experiments of Dusser de Barenne. The projection of the face is of the "onion-skin type" with concentric zones on the face being successively represented, the buccal cavity being lowest. On the whole the overlap in the cortex is no greater than the peripheral overlapping of dermatomes, and seems largely caused by the peripheral overlap. Finally an important result is that the highly sentient hand projects to an area of the cortex relatively much greater than that devoted to the trunk or leg despite the lesser area of skin.

DESTRUCTION OF PARIETAL LOBES

Studies of the effect of ablation divide into two categories: (1) those in which the sensory status of an animal is inferred from observations of movements in response to stimulation, and (2) those involving discrimination of sensory stimuli as a learned performance. Early studies of both types were not particularly fruitful and have been reviewed in detail elsewhere (Ruch, 1935). Some of the obstacles met in earlier work on the sensory function of the cortex lay, not only in the difficulty of testing sensation in animals, but also in the fact that the technique for making sharply circumscribed lesions had not become sufficiently developed in experimental laboratories to allow a close correlation between the ablation of a restricted cytoarchitectural field and disturbance of a specific function. Combination of the newer training techniques of comparative psychology (the conditioned reflex, the problem-box and discrimination procedures) with the techniques of modern neurosurgery has made possible a wholly new type of controlled experiment. Though not completely objective, the hopping and placing reactions have proved of greatest value in the study of parietal function.

HOPPING AND PLACING REACTIONS (chs. x and xx). These reactions according to the study of Woolsey and Bard (1936), not yet published in full, depend upon the cerebral cortex both in their sensory and motor aspects. Contact placing consists of a precise placement of the foot on a table top when the dorsum is brought into light contact with the edge of the table, vision being excluded. This response is completely and permanently lost after removal of the postcentral gyrus; the effect is entirely contralateral to the ablation. Failure of the reaction is not the result of cortical motor impairment since the affected limb can be caused to place by restraining the opposite limb and touching the opposite side of the face to the table (crossed placing). The hopping reaction is only temporarily if at all influenced by removal of the postcentral gyrus, according to Woolsey and Bard (1936), and is presumably maintained by the motor areas.

A more recent study by Kessler and Kennard (1940) implicates a wider extent of cortex in both reactions. Whereas ablation of the postcentral gyrus only transiently abolishes the placing reaction a parietal lobectomy does so permanently. The latter procedure has a lesser yet definite, enduring effect on the hopping reaction. It is reasonable, as Ruch and

Kasdon(1943)point out, that these reactions should be somewhat more focally represented than weight discrimination(see below). The latter is a discrimination of intensity, whereas placing and hopping reactions both have a definite spatial element. Thus when the dorsum of the foot touches the table the foot moves forward, when the side is touched the foot moves to that side, etc. This spatial element may make the reaction dependent on a relatively few, specific neurons of a topographically organized projection such as the postcentral gyrus possesses.

DISCRIMINATION STUDIES IN MONKEYS AND CHIMPANZEES. The effect of parietal lobe lesions upon the capacity of monkeys and chimpanzees to discriminate between differing weights, geometrical shapes(stereognosis), and the texture of rough surfaces has been studied by Ruch(1935, 1936). In his first experiments he used monkeys trained to discriminate slight differences in weight. The conclusions drawn were based upon tests of sensory status made 3 or more weeks after operation and after considerable retraining. He found that removing area 4, the postcentral gyrus, or the posterior parietal lobule, separately in the monkey resulted in an initial impairment in weight discriminatory capacity, which was subject to recovery; in fact, the experiments yielded the unexpected result that the ability to discriminate differences in weight returned to the preoperative level, and this was true of bilateral as well as unilateral lesions. In view of the heavy thalamocortical projection to areas 4 and 6, the lesions were extended into the precentral convolution; these were necessarily subtotal, since complete lesions, even of area 4, when combined with postcentral damage, induced a disabling ataxia and paralysis. Primary ablation of area 4 was without effect on weight lifting(fig. 88). When a lesion of area 4, which was subtotal but nevertheless destroyed the area of heaviest thalamocortical projection, was added to a primary postcentral lesion, no disturbance of weight discriminatory ability could be detected. On the other hand, a monkey in which posterior parietal and postcentral lesions were combined exhibited grave ataxia and inability to discriminate weights ineffaceable by training(fig. 88). From such experiments it was concluded that weight discriminatory ability is not focally localized in either of the 2 subareas of the parietal lobes. The parietal lobes, though essential for the discrimination of small weight differences, are not the sole areas of representation of this function. Bilateral parietal lobectomy was not studied. Since the sensory capacity underlying weight discrimination appeared to be notably less "encephal-

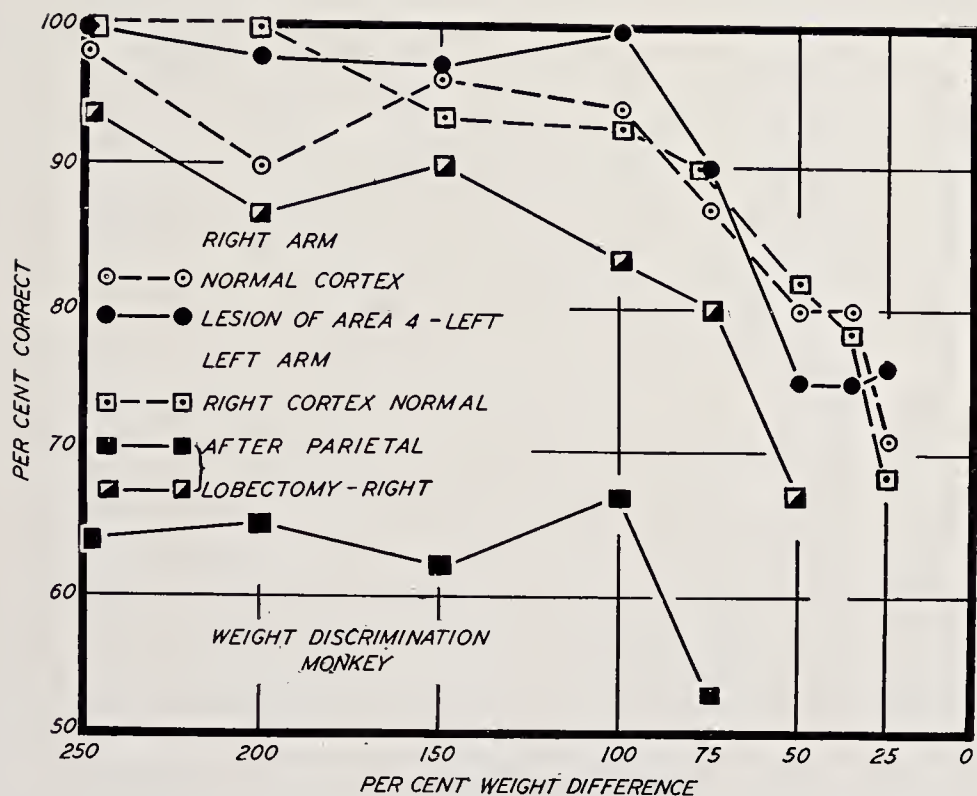


FIG. 88. Discrimination of lifted weights by monkey after lesion of area 4 and after complete parietal lobectomy. Severe initial disturbance (filled squares) following lobectomy is lessened by further training (half-filled squares) but a residual defect remains. Compare with curves for parietal lobectomy in chimpanzee below. Curves also show that a primary lesion of area 4 is without effect on accuracy of weight discrimination.

ized" in the monkey than in man, Ruch carried out a similar series of experiments upon the chimpanzee, which stands midway between man and monkey in its cortical development.

In the chimpanzee, Ruch finds that ablation of the postcentral gyrus and the posterior parietal lobes separately has given rise to defects in weight and roughness discrimination. Yet neither area can be said to contain a focal representation of weight or roughness discrimination, since the defects are largely effaced by retraining. With complete parietal lobectomy, weight discriminatory capacity, roughness discrimination and stereognostic capacity are permanently impaired, although not completely abolished (fig. 89 and 90).

Weight discrimination. In the accompanying figures, the weight differences are expressed as a percentage of the standard weight. With complete ablation of areas

3-1-2, no permanent effect could be detected in weight discriminatory ability (fig. 89). With ablation of the posterior parietal lobule, however, there was a much more severe initial deficit, but with retraining after a lapse of two and a half months the preoperative level of performance was virtually regained (fig. 90). With complete parietal lobectomy, the disturbance was again more profound than after the posterior lobule lesion, the animal failing completely to discriminate a 100 per cent weight difference (filled square). A large deficit existed after more

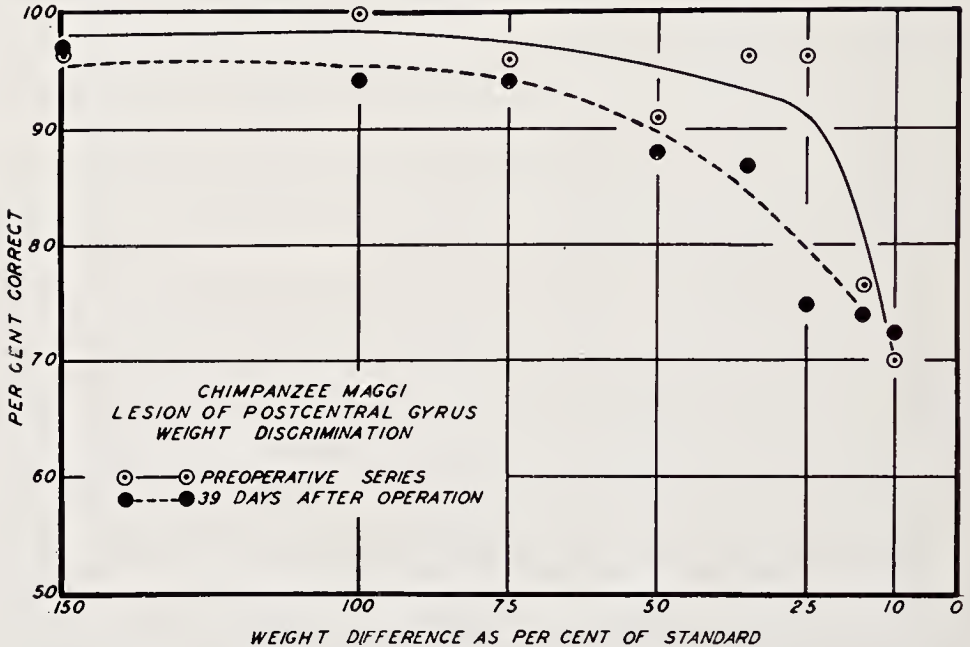


FIG. 89. Discrimination of lifted weights by chimpanzee after ablation of postcentral gyrus. Graph shows per cent of trials (ordinates) in which successively smaller weight differences, expressed as a per cent of standard (abscissae), were successfully discriminated. The 50 per cent ordinate represents a chance performance. Points for 10 and 15 per cent weight difference are based on a large number of observations and establish absence of significant reduction in performance.

than six months and was not improved by training (dotted circles). Both the postcentral gyrus and the posterior parietal region are clearly involved, although ablation of them separately may give rise to little deficit. These observations suggest that weight discrimination may depend more upon the posterior parietal lobule than upon areas 3-1-2.

Roughness. The discrimination of roughness has been studied in the same animals described in figures 89 and 90 and the results are closely similar. A lesion of the postcentral gyrus was without effect when tested 44 days after operation (compare fig. 89). Posterior parietal lesions produced somewhat greater deficit, which, however, was far short of that following complete parietal lobectomy (compare fig. 90).

Geometrical forms. A chimpanzee, trained to discriminate by palpation (in darkness) between geometrical forms such as pyramids, wedges and cones, regained after a considerable period of training (posterior parietal lobule removed) his ca-

capacity to distinguish a cone from a pyramid, but never regained a capacity to discriminate between a pyramid and a wedge. This again points to the posterior parietal lobule as important in higher levels of the sensory process.

These observations taken together indicate that in both the chimpanzee and monkey these higher discriminatory capacities, although largely subserved by the parietal lobes, are not localized in any single portion of

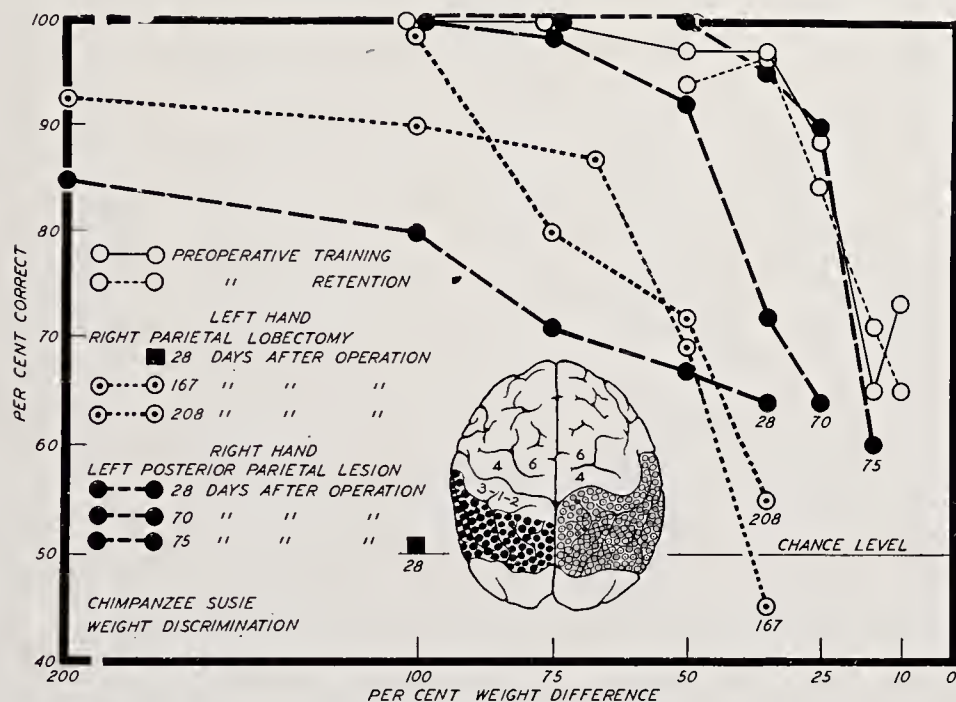


FIG. 90. Discrimination of lifted weights by a chimpanzee after ablation of the posterior parietal lobule and after parietal lobectomy. Note recovery shown after the subtotal operation (solid circles) and contrast with absence of improvement in two series after parietal lobectomy (dotted circles). The two preoperative curves (unfilled circles) demonstrate the accuracy of the observations.

it; that tactual and proprioceptive functions are not separately localized; and that the parietal lobe is not the sole locus of sensory representation for the contralateral hand. The difference between monkey and chimpanzee lies in the depth and persistence of impairment from corresponding lesions, denoting a higher degree of encephalization in the latter form. When tested by similar procedures, the performance of human subjects with parietal lesions suggests that the organization of the human parietal cortex resembles that of the chimpanzee, the difference again being one of degree (see below).

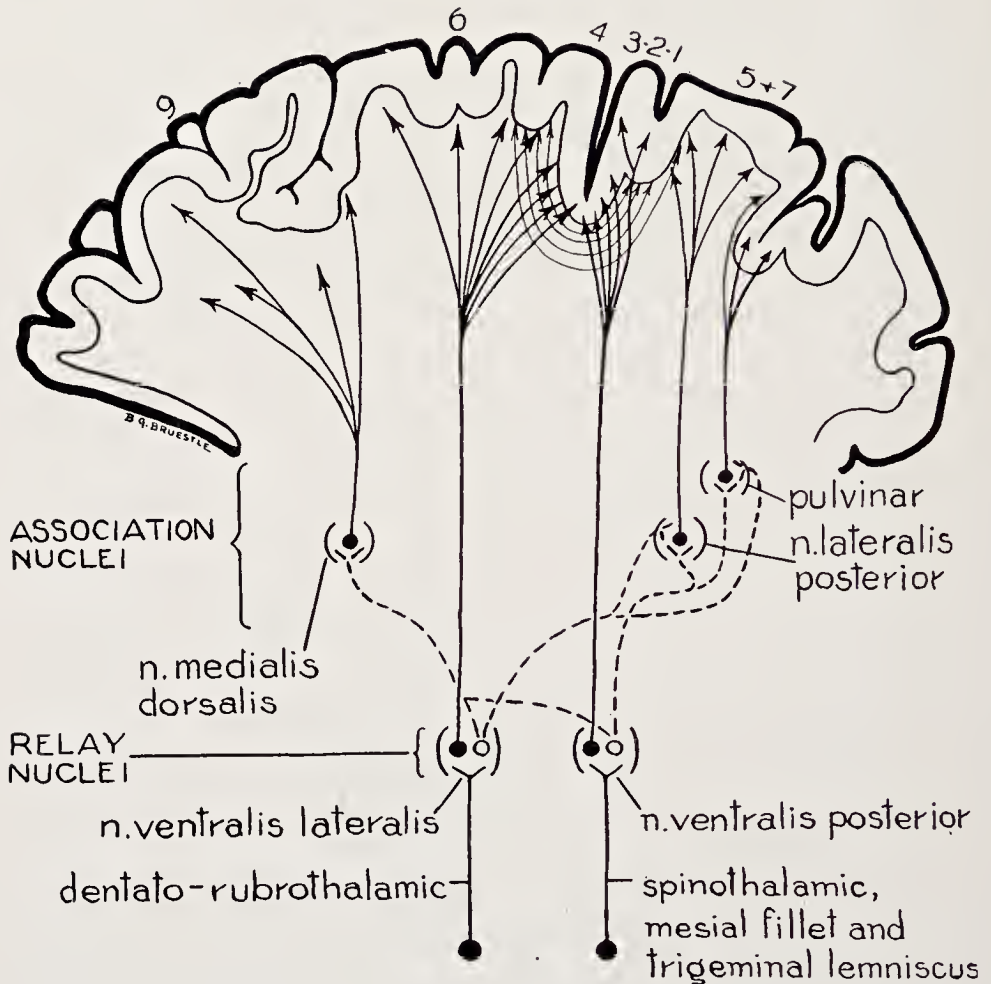


FIG. 91. Diagram showing the principal thalamocortical projections and connections of the thalamic relay nuclei with ascending projections, based upon the work of Walker and of Le Gros Clark. Note the extent of parietal and frontal cortex receiving projections. The dotted lines represent intrathalamic connections, the details of which are not fully known. (From Ruch and Kasdon, unpublished.)

The following interpretation of the experiments upon monkeys and chimpanzees can then be taken to apply to man as well. The experiments are difficult to interpret by the traditional concept of a postcentral region which receives all sensory impulses and transmits them to the posterior parietal association area. Interruption of such a chain either anteriorly or posteriorly in the parietal lobe would be equivalent to parietal lobectomy, but such is not the case. Both subregions appear capable of independent function, which implies that the posterior parietal

lobule receives a separate projection. For this there is definite anatomical evidence. Walker (see fig. 91) has demonstrated in the thalamus a "bypass" whereby impulses from the ascending sensory systems travel via relay nuclei through association nuclei to the posterior parietal lobe.

The locus of the discriminatory ability demonstrable after complete parietal lobectomy if sufficient time for recovery and retraining is allowed may lie in the motor areas; or less probably in the parietal lobe of the same side as the hand tested; or in the thalamus. Participation of the motor areas is virtually impossible to demonstrate by cortical ablation experiments because of the resulting paralysis of fine voluntary movement. Sjöqvist and Weinstein (1942) have attacked this problem by differentially interrupting the afferent input to the parietal and frontal lobes below the thalamus where sensory fibres are not intermingled with motor pyramidal tract fibres. Just as with parietal lobectomy, weight discrimination and other proprioceptive functions are not greatly and permanently impaired by section of the medial lemniscus. Section of the dentato-rubro-thalamic tract, though as a primary operation is without conspicuous effect, when added to a lemniscal section produced impairments much greater than lemniscal section alone. Therefore it may be argued by analogy that the residual ability following parietal lobectomy is subserved by the motor areas.

CLINICAL STUDIES

The studies of Head and Holmes (1911, 1918) remain virtually without parallel in clinical literature as an attack on the *physiology* of the human cerebral cortex. As Holmes (1927) points out, the freshness of Head's point of view lay in asking not whether a sensation was lost, diminished or spared by a cortical lesion, but what qualities of sensation are localized in the cerebral cortex. Naturally this required great refinement of sensory examination in order to explore the same modality of sensation at various levels of perceptual elaboration. Head's studies are notable too for their emphasis on phylogenetic or evolutionary principles.

Head departs from most clinical observers by believing that certain aspects of sensation — mere recognition of pain, temperature, heavy contact, etc. — are subserved by the thalamus. The discrimination of fine grades of sensation and, more particularly, the gnostic aspects of sensation represent the cortical contribution. As a corollary, a sense modality

like pain which is poorly developed in its cognitive qualities will be less influenced by cortical lesion than will touch or kinesthesia. Thus, anesthesia can never result from a cortical lesion, the reports to the contrary(not infrequent in clinical literature)being due to shock or damage to subcortical structures. Patients with parietal lesions, although aware when stimulated and able to name objects, characteristically fail to appreciate weak stimulation or to discriminate fine differences in intensity; fails to localize it correctly(topognosis)or to distinguish a single from two adjacent impacts(two-point threshold); and finally is unable to combine information from the several sense modalities for recognition of the shape and nature of an object in contact with the skin(stereognosis). Similarly, a gross passive movement or the presence of a heavy weight in the hand may be recognized, but " the recognition of the position of the limbs in space, the appreciation of movement and the recognition of its direction and range, as well as the discrimination of weight, are those forms[levels]of sensation which are most commonly and most severely affected by lesions of the cerebral cortex "(Holmes, 1927). Head, although little interested in the details of localization within the cortex, introduced a concept which will probably prove fruitful in this field, *i.e.*, that it is not the several somatic senses, but *levels* of sensation that are separately localized. Final decision between these alternatives demands a vast amount of experimentation, employing objective, quantitative tests of each sense modality at several levels of complexity.

Quantitative studies of sensory disturbance in man have seldom been made; indeed, there is no record in the literature of a single quantitative determination of weight discriminatory ability in cases of parietal lesions. On account of this, Ruch, Fulton and German(1938)subjected a group of 4 patients with parietal lobe damage to an extended series of weight discrimination tests similar to those used with chimpanzees. Two of these cases are of particular interest, because the lesions were surgical and complementary, one being anterior in the parietal lobe and the other posterior. Both lesions resulted in decreased ability in such tests as the discrimination of roughness and of weight with the supported and unsupported hand and hence gave no evidence of a zonal localization of sense modality. This was exactly the result obtained in comparable chimpanzee experiments. The impairment in no one of these 4 cases was as great as in the chimpanzee after complete parietal lobectomy. Weight discrimination with the hand unsupported, which

primarily tests muscle sense, was less disturbed than was discrimination with the supported hand, which is therefore a more sensitive test of parietal lobe damage (fig. 92).

Ablation studies in trained monkeys and chimpanzees indicate that lesions of the postcentral convolutions (areas 3-1-2) or the posterior pari-

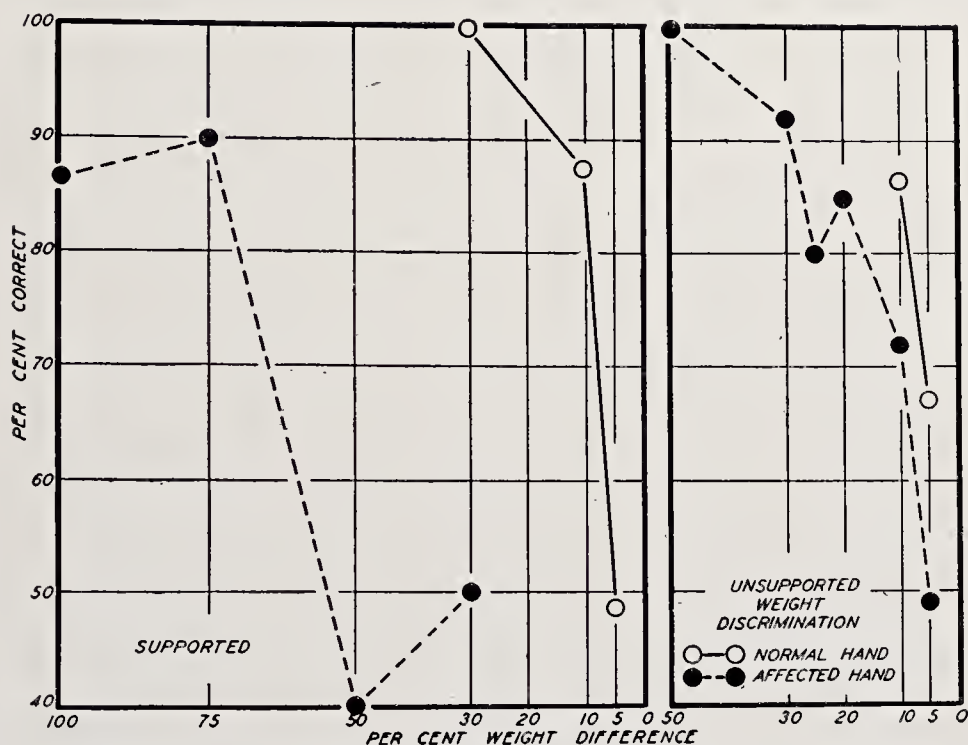


FIG. 92. Discrimination of weight by a patient with a surgical lesion (subtotal) of the posterior parietal lobe. The deficit in unsupported weight lifting is definite, but quantitatively slight.

etal lobule (areas 5 and 7) separately reduce only transiently the ability to discriminate fine differences in weight, yet total parietal lobectomy is followed, in both forms, by a permanent defect. Thus, in the monkey and chimpanzee there is no focal representation of such functions *within* the parietal region, which is nevertheless the main area of representation of these functions. Comparable studies indicate that these functions are also not focally localized in the human cortex, although the disturbances are greater initially and more enduring. Monkey, chimpanzee and man, therefore, represent a series in which increase of corticalization has occurred during phylogeny.

In right-handed human beings, lesions of the left angular gyrus produce profound disturbances in the speech mechanism (sensory aphasia), accompanied by various psychical disturbances, *e.g.*, finger agnosia.

SUPRAMARGINAL AND ANGULAR GYRI IN RELATION TO SPEECH DISTURBANCE. Peculiar to the human being are speech disturbances, prone to develop in right-handed individuals with lesions in the inferior part of the left posterior parietal lobule, a region far more highly developed in man than in any of the lower animals. These speech disturbances fall into the general category of "sensory aphasia." It is beyond the scope of a physiological text to discuss in detail the disturbances of higher intellectual functions which follow cerebral lesions. However, no account of the parietal lobe would be complete without some mention of Wernicke's (1874) type of aphasia, associated with lesions of the left angular gyrus in right-handed human beings. Pierre Marie (1922), who has studied many such cases, points out that the effective lesion usually involves not only the angular gyrus, but also the base of the first and second temporal convolutions. With such lesions, patients can speak, but their intellect is generally impaired to a marked extent, and they are likely to talk nonsense (aculalia). Although they are able to "write" in the sense of copying, they have serious difficulty in writing spontaneously. Most conspicuous in these cases is an incapacity to comprehend spoken or written language. Wernicke's aphasia was also studied at great length by Head, who in 1920 published his two-volume treatise on the subject. Head, as in his studies of other phases of sensation, concerned himself less with localization and more with accurate characterization of the generalized cortical functions which had become impaired. He maintained that strict localization was impossible, because in the higher intellectual sphere there were wide differences in organization of conceptual processes from one individual to the next. He believed, however, that large lesions in the posterior parietal lobe tended to produce verbal and nominal aphasia. Head's classification of the aphasia is as follows: (i) *verbal aphasia*, in which there is a defect in word formation; (ii) *nominal aphasia*, or disturbance in the use of names and in the capacity to name objects (anomia); (iii) *syntactical aphasia* (aculalia), in which the patient tends to talk jargon; and (iv) *semantic aphasia*, in which the content of a paragraph or a situation cannot be grasped; words and sentences are correctly read, spoken and written, but reflect lack of comprehension.

Special manifestations of these intellectual disturbances continue to multiply in the literature of clinical neurology. Thus, in 1924, Gerstmann described a new syndrome of "fingeragnosia" characterized by a total inability to recognize, indicate on command, name or choose the individual fingers of the patient's own hands or the hands of others. In Gerstmann's first case, the patient was unaware of the difficulty. The phenomenon has been studied by Lange (1930), Muncie (1935), and by Nielsen and Fitzgibbon (1936), and has attracted widespread interest. But it is almost certainly a special manifestation of intellectual deficit accompanying Wernicke's aphasia, no report having indicated that the symptoms exist as an isolated entity. Entirely similar are the recent reports of Schilder (1934) on the failure of localization of the body image. Patients with large lesions of the left supramarginal and angular gyri entirely lose awareness of the existence of the opposite half of the body or of individual members, such as the hand, ear or leg. A patient, for example, may vehemently insist that his own hand is not his, and that it belongs to someone else.

CENTRAL REPRESENTATION OF TASTE

The cortical representation of taste is usually described as overlapping or adjacent to that of olfaction which is stated to lie in the hippocampal gyrus. Upon examination of the literature it is difficult to find adequate experimental justification for this belief, apart from a few early experiments by Ferrier. The generally accepted localization seems little more than an inference based upon the close psychological relation between taste and smell, which are always confused by naive subjects, and upon the fact that they are both "chemical" senses and both connected with feeding reflexes and behaviour. Topography rather than function is often the determinant of the structural organization of the nervous system. At any rate, as Börnstein(1940)originally showed from a study of war-injury cases, the cortical taste area appears to be located at the foot of the sensory area(face region)adjacent to or overlapping the locus for somatic sensation from the tongue. This places taste close to the motor centres for mastication and deglutition, to which taste must be closely related.

The evidence for this new localization of taste is as follows:(i)taste disturbances over the contralateral half of the tongue were found by Börnstein(1940)to be associated with slight hearing defects, hypaesthesia of the face and disturbances of mastication, all functions localized near the opercula of the Sylvian fissure;(ii)taste disturbances from bilateral lesions of the foot of the sensory area have been demonstrated by Börnstein and by Patton and Ruch(1943);(iii)Horsley-Clark lesions of the thalamic nucleus which projects to the face region of the sensory area cause severe objective disturbances of taste(Blum and Ruch, 1943); and (iv)gustatory hallucinations have been evoked by stimulation and epileptic seizures originating in this region and Penfield and Erickson (1941)localize taste sensations just below other tongue sensation.

From the evidence it seems that taste must be added to general somatic sensation in cataloguing the functions of the parietal lobe. Many problems of the finest detail of the taste pathways remain to be worked out. For example, the nuclear origin and course of the secondary gustatory neurons, long a subject for discussion, may be determined by retrograde degeneration studies now that the site of the thalamic relay for taste is known.

SUMMARY

Anatomical studies of thalamocortical projection have greatly assisted in understanding localization of somatosensory function. The area of cortex receiving thalamic projections extends over the whole parietal lobe and over the motor areas of the frontal lobe. Within this field three sub-regions are distinguished on the basis of the thalamic origin of the projections. The projections to areas 4 and 6 derive from the cerebellum and ultimately the spinocerebellar tracts. The relay nuclei of the thalamus which project to the postcentral gyrus receive the great ascending somatosensory tracts of the spinal cord; this projection is topographically organized and conducts some impulses from the ipsilateral half of the body. Areas 5 and 7, the posterior parietal lobule, receive fibres from thalamic association nuclei (pulvinar and lateral nucleus) which in turn receive impulses from sensory tracts via relay nuclei.

Electrical stimulation of the human cortex and strychnine stimulation of macaque and chimpanzee cortex disclose a topical arrangement into face, arm and leg areas and that sensation is elicited from the motor areas as well as the parietal lobe. Local application of strychnine to the cortex gives rise to sensory disturbances — paresthesia, hyperalgesia and hyperesthesia — which in deep structures are entirely contralateral, but in cutaneous fields are bilateral. Local strychninization fires or depresses activity of other cortical areas and tends to fire off certain nuclei of the thalamus.

Correlation of the areas of the cortex becoming electrically active when various regions of the skin are stimulated proves that the body surface is projected dermatome by dermatome upon the postcentral gyrus. The serial order is that of the dorsal nerve roots of the spinal cord except that the cervical segments appear in reverse order.

Hopping and contact placing reactions depend upon the sensory cortex. The parietal lobe, and in large part the postcentral gyrus, subserve contact placing, whereas the hopping reaction depends more upon the prerolandic cortex.

Taste has recently been added to the functions of the sensorimotor area, and is localized in the region of the face representation.

XX

CEREBRAL CORTEX: THE MOTOR AREAS AND PYRAMIDAL SYSTEM

HISTORICAL NOTE

The existence of a motor area was suggested by an early clinical observation of Robert Boyle (1691, pp. 67-73), who recorded the remarkable case of a knight who, following a depressed fracture of the skull, experienced an enduring "dead palsy," *i.e.*, motor and sensory paralysis, of the arm and leg; eventually a surgeon explored the wound and the motor and sensory symptoms disappeared within a few hours after a spicule of bone pressing on the dura had been removed. No further cases of this type found their way into literature until the nineteenth century. Indeed, there was little suggestion of a motor area until 1864 and 1870 when Hughlings Jackson, on the basis of his study of "focal" epilepsy, predicted that an area existed in the cerebral cortex which governed isolated movements. This brilliant clinical deduction was followed almost immediately by experimental verification, for in 1870 Fritsch and Hitzig discovered that electrical stimulation of the frontal cortex of various mammals caused movements of extremities on the opposite side; and in 1874 Hitzig published his monograph on the cerebral cortex in which he accurately defined the limits of the motor area both in dog and monkey. This was followed by Beevor and Horsley's (1890a&b) various papers on the excitable cortex of monkey and orang. In 1873, David Ferrier, while serving at the West Riding Lunatic Asylum,* studied the motor area of monkeys, and by removal of an excitable region such as the "hand area" caused paralysis of the hand itself (1873, 1875). Ferrier gave a demonstration of his hemiplegic monkeys at the International Medical Congress of 1881 (London), and the similarity of their symptoms to those seen in man following hemiplegia was so striking that the French neurologist, Charcot on seeing the monkey's arm, exclaimed, "It is a patient!" At the same meeting Goltz exhibited his decorticate dogs; from this and other demonstrations at the Congress Sherrington received an initial stimulus of his life's work, and he soon (1884) published his first scientific paper on the spinal degenerations observed in Goltz' dogs. In 1899 Talbot of North Dakota working in Ewald's laboratory stimulated the motor cortex of conscious dogs through the use of implanted electrodes and succeeded in producing focal seizures similar to those described in clinical cases by Jackson. In the years that followed, the motor area was studied by many investigators, the most outstanding work being that of Grünbaum and Sherrington which, although initiated by Sherrington in the early nineties, remained unpublished until 1901-03 (fig. 93). Later work by Leyton [Grünbaum] and Sherrington, recounting their experience with the motor area of chimpanzees, orangs and gorillas, was finally published in 1917. Thereafter the

* Sir James Crichton-Browne who, as Director of the West Riding Asylum, invited Ferrier there to carry out his experiments, died January 31, 1938, as the first edition of this book was passing through the press — at the age of 97 years.

subject largely rested until 1925 when Foerster and the Vogts(1926)published their illuminating papers on the motor fields of the human brain(see Foerster, 1936).

The human cortex was first stimulated by Bartholow in 1874; later by Sciamanna(1882), Horsley(1887), Keen(1888), Nancrede(1888), Beever and Horsley (1890)and by Bidwell and Sherrington(1893), and it was evident from the ob-

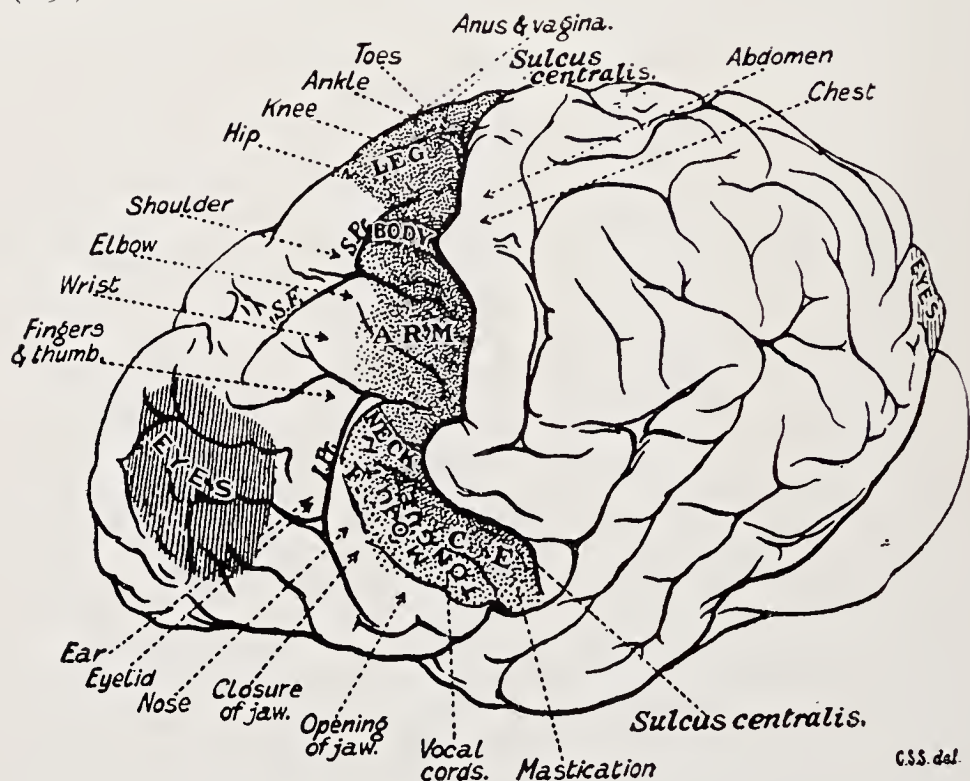


FIG. 93. Map of motor area of chimpanzee including frontal and occipital eye fields. Other foci of discrete responses are indicated on chart. Note that representation of anus and vagina occupy the same relative positions as tail area in spider monkey shown in figure 94(Grünbaum and Sherrington, *Proc. roy. Soc.*, 1901, 69B, 208).

servations of these pioneers that the distribution of excitable foci in man corresponded roughly to that of animals(for details, see Lamacq, 1897, and Penfield and Boldrey, 1937). Our concepts concerning the motor areas of man and animals have been extensively modified during the past decade by the investigations of the late J. G. Dusser de Barenne and his colleagues on the organization of the cerebral cortex and the interrelation of its various functional areas. The details of these new developments will be included in the revised version of this and the following chapter.

THE studies of Hitzig, Ferrier and Sherrington on the cerebral cortex of animals, and those of Foerster and others on man, indicate that many

parts of the cerebral mantle influence the activities of subcortical and spinal centres; the region from which this motor influence may be most readily demonstrated lies in the precentral convolution, coinciding cyto-architecturally (ch. xv) with the *area gigantopyramidalis* (area 4 of Brodmann); and it might be anticipated, even in the absence of direct proof, that this unusual excitability is to be attributed to the gigantic cells of Betz. Under certain anesthetics (*e.g.*, dial) the excitable region of the cortex is sharply restricted to area 4, but under light ether and the local anesthetics the anterior margins of area 4 cannot be accurately determined by stimulation, since the posterior part of area 6 is also readily excitable, and its excitability merges imperceptibly with that of area 4. But because area 4 is the region of greatest excitability and also the region essential for isolated motor responses it seems proper, as A. W. Campbell (1905) originally pointed out, that it should be designated "the motor area." This allows the use of the convenient term "premotor area" for area 6 (ch. xv), the adjacent motor field (Fulton, 1935). It is understood that area 4 is in connection with many, perhaps all, other areas of the cortex and that it serves somewhat as a funnel through which many varieties of highly organized movement-patterns are ultimately discharged. The characteristics of this "final common path" from the cerebral cortex, therefore, deserve careful study.

EXCITABILITY OF AREA 4

GENERAL CHARACTERISTICS. The excitability of area 4 in higher primates and man differs from that of other motor regions of the cortex in the discreteness of its responses. A mosaic of circumscribed foci can readily be demonstrated along the caudal surface of the precentral region from which, on electrical stimulation, isolated contralateral movements, sometimes of single muscles but more often of synergic muscle groups, can readily be obtained; individual responses may be evoked in such muscles as biceps, triceps, flexor longus digitorum and, in man, even a single interosseus muscle may respond. By contrast, from area 6 and especially from area 6 $\alpha\beta$ (ch. xxi), complex patterns of movement are obtained involving an entire extremity. Comparable stimulation of other excitable fields of the cortex indicates that area 4 is the only one, except for the frontal eye fields (area 8), from which genuinely isolated movements may be obtained.

"OPTIMAL" STIMULI. In nearly all studies of the excitability of the cerebrum a simple faradic stimulus has been used, generally from a coreless induction coil, applied either with a monopolar electrode (diffuse electrode in the rectum), or with bipolar electrodes the points of which were separated by 1 to 2 mm. More satisfactory results have been obtained with a 60 cycle alternating current giving a series of individual pulses approximately 8 msec. in duration and of varying intensities. The characteristics of excitability of the cortical neurons in terms of strength-duration curves have also been closely studied. Wyss and Obrador (1937)

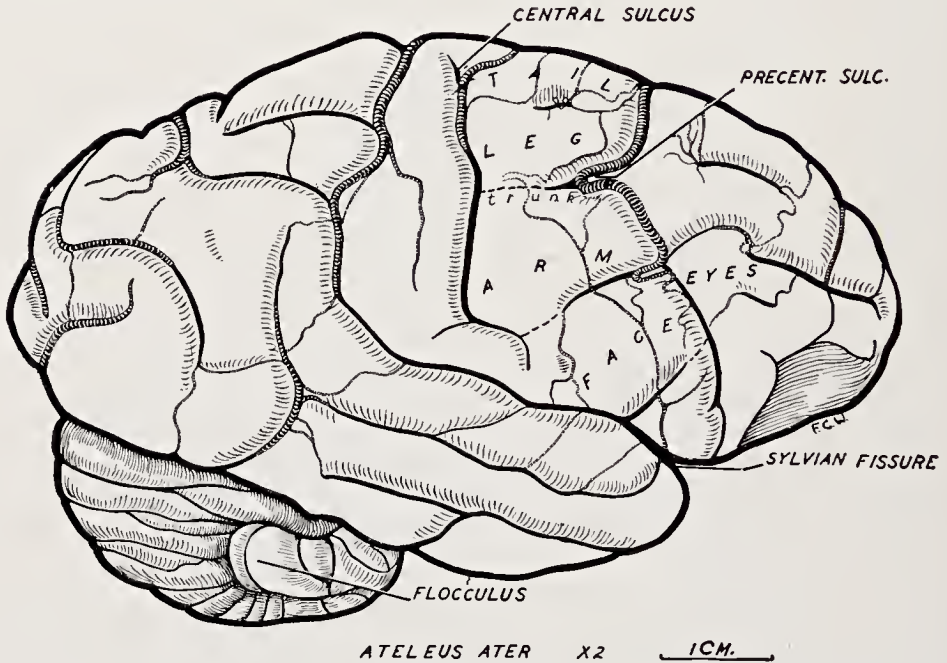


FIG. 94. Right hemisphere of spider monkey showing motor area with relative position of tail, leg, arm, face and eye fields. Note that the tail area occupies as much space as the leg representation (Fulton and Dusser de Barenne, *J. cell. comp. Physiol.*, 1933, 20, 408).

have investigated the stimuli adequate for the cerebral cortex of the macaque, comparing the excitability of the motor and premotor areas under dial and light ether anesthesia. Their principal observations were as follows: single motor foci of area 4 react to a single stimulus by a short twitch of the affected muscle. The optimal duration of current has a rising phase lying between 7 and 20 msec., corresponding to a full wave duration of approximately 35 to 100 msec. The higher values were found for proximal movement, whereas the shorter optimal stimuli were adequate for discrete distal movement, especially of the fingers. In one experiment 7 msec. sufficed for the index finger, while 15 were required for flexion of hip. The chronaxie of these points proved to be 1 msec. for the index finger, and approximately 2 msec. for hip flexion. It follows from this that the adequate stimulus for the motor cortex is far longer than that ordinarily obtained from a coreless induction coil. For such a stimulus to be effective, a very high stimulation voltage must be used which inevitably causes spread of stimulating current. The beautifully discrete responses obtained by Wyss and Obrador indicate in a strik-

ing manner the inadequacy of older forms of stimulation. The optimum frequency for stimulation of area 4 would, according to Wyss and Obrador's results, lie not higher than 25 cycles per second, insofar as shape and duration of each wave is concerned. It is possible, however, that the phenomenon of facilitation may make feasible the use of somewhat higher values (Boynton and Hines, 1933; Dusser de Barenne and McCulloch, 1939a).

PROOF THAT BETZ CELLS ARE PRIMARILY RESPONSIBLE FOR EXCITABLE PROPERTIES OF AREA 4. That the giant pyramidal cells of the fifth layer in area 4 are largely responsible for the excitable properties is indicated by three lines of evidence: study of (i) infant monkeys, (ii) laminar coagulation, and (iii) transection of the medullary pyramids.

Stimulation of cortex in infants. During the first few weeks of life, it is generally difficult in the infant macaque to obtain isolated motor responses, even with strong stimulation of the cortex. This is undoubtedly to be correlated with the fact that the Betz cells at this time are still relatively undifferentiated (pear-shaped) and to the fact that the pyramidal tracts themselves are not yet completely myelinated. Myelination probably becomes established in the macaque between the first and third months (later than in the kitten, Langworthy, 1927), but excitability is established before myelination is completed. Similar observations have been made on the human infant, although the exact time at which isolated responses appear from stimulation of area 4 has not yet been determined in man (Hines, 1942; Kennard and McCulloch, 1943).

Laminar coagulation. Dusser de Barenne (1934a&b) has introduced a new technique for destroying successive cortical laminæ. Application to the cortex of a metal surface heated to 80° C. for 5 secs. kills all 6 cortical layers; if a part of area 4 of a macaque is coagulated in this manner, its excitability is completely abolished (Dusser de Barenne and Zimmerman, 1935). Exposure at 70° C. for 3 secs. kills only the outer 3 or 4 layers, and in these circumstances the excitability of area 4 remains essentially unchanged. On the basis of this evidence, it was concluded that the excitable properties of area 4 of Brodmann are due to the large and giant pyramidal cells in the fifth cortical layer. The effect of laminar coagulation of area 4 on the spontaneous action current rhythm (of Berger) has been studied; the electrical activity of the intact cortex is an algebraical summation of electrical effect of all the layers. The dominant alpha rhythm of area 4, however, is unchanged by destruction of the outer 3 layers (chronic experiments).

Medullary transection of pyramids. The medullary pyramids have been successfully transected by a number of authors (Rothmann, 1902, 1907), most recently by Marshall (1933-36), and by Tower (1935, 1940). Following such an operation, area 4 loses entirely its capacity for individualized response; the characteristics of the excitability which remains will be discussed at the end of this chapter. The evidence from young animals, the laminar coagulation studies, and the retrograde changes in the Betz cells (with concomitant changes in excitability) following medullary section of the pyramids thus constitute proof that the corticospinal neurons whose cell bodies lie in the fifth cortical layer are responsible for the peculiar excitable properties of area 4.

It has been assumed by certain writers that the length of the axons of the corticospinal neuron is to be correlated with the size of cell body. Thus, the Betz cells in the foot area are larger than those in the arm, and very much larger than those in the face area. However, from the analogy with the motor unit of the anterior horn cell, it is more probable that size of cell body is to be correlated, not with length of the axons, but with the size of the motor unit which it innervates.

A single pyramidal tract fibre undoubtedly innervates more than one internuncial neuron in the spinal cord, and some probably innervate many; others few. One would expect the smaller unit to have smaller cell bodies (ch. xv).

The distribution of excitable points in area 4 follows a characteristic pattern throughout the vertebrate series, representation of the tail and foot being found near the midline, the trunk and arm more laterally

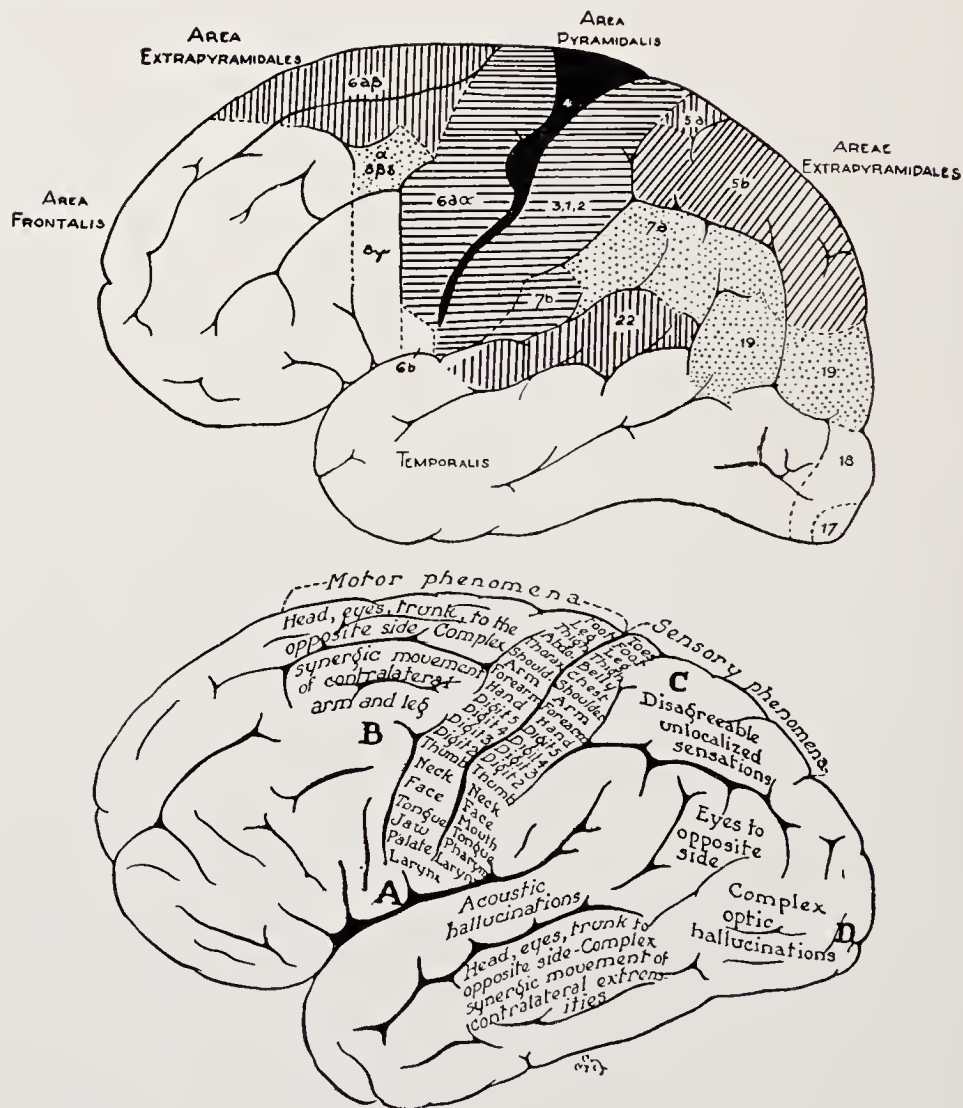


FIG. 95. Motor area of man correlated with principal cytoarchitectural fields. Above, Foerster's cytoarchitectural map of the human brain. Below, Foerster's map of same cortex indicating principal excitable foci as determined by direct stimulation of brain under local anesthesia.

and the face more laterally still, as can be seen in the accompanying illustrations of monkey, chimpanzee and man (figs. 93-95). As in the case of sensory representation, the motor foci also assume a roughly dermatomal arrangement. In spider monkeys (fig. 94) which have prehensile tails, the motor representation of the tail is as large as that governing the foot. The perineal musculature, including the sphincters of the vagina and anus, as well as those of the bladder, also have discrete representation in man in the superior part of area 4 (medial surface of the hemisphere facing the falx) (Frankl-Hochwart and Fröhlich, 1902). The discreteness of the cortical foci in area 4, *i.e.*, the number of separately excitable points, is much greater in the higher apes than in monkeys (except possibly the spider monkey), and greater in man than in the anthropoids. From the face area, for example, it is possible to evoke isolated movements at the corner of the mouth, protrusion and withdrawal of the tongue, coning of the lips, elevation of the soft palate, movements of the vocal cords, etc. Vocalization does not ordinarily occur from stimulation of area 4 in animals. In man, however, it may be evoked consistently from a small focus in area 4c. Its response consists of a continuous cry or grunt which the patient is quite unable to control. From foci slightly rostral to this inhibition of volitional vocalization is readily evoked (Penfield and Boldrey, 1937).

Although roughly dermatomal, the varying extent of representation of the distal as opposed to the proximal joints precludes any simple dermatomal basis of cortical representation — the thumb, for example, is governed by an area ten times greater in extent than that for the thigh. However, there is no doubt that organization of the motor and sensory projections of the cortex reflects the segmental origin of the nervous system. The sensory systems of the dorsal columns, fillets, thalamus and parietal lobe all retain their spatial organization originating in the spinal segments (Foerster, 1927b; Woolsey and Walzl, 1942); the corticospinal system retains similarly a distinctly metameric topography evident in the internal capsule, peduncle and in its lamination in the spinal cord. Hence it is possible from the cortex of any higher primate to evoke *segmental* movements involving few and sometimes quite isolated muscles.

FOCAL SEIZURES. A characteristic of the excitability of area 4 is the tendency of the response from a single focus to *spread* on mere continuance of an unaltered stimulus. Thus a relatively weak stimulus applied to the area producing thumb movement will, if it persists, spread to excite movements of the fingers, forearm, shoulder, possibly to the corner of the mouth and to other parts of the face; if the stimulus is strong, the response may spread even to the lower extremity. When a focal stimulus

of this character is very strong, it may, even though applied briefly, lead to a focal epileptic seizure of the type which Hughlings Jackson originally described in clinical cases — still known as “Jacksonian seizures.” Particularly striking experimental seizures of this sort have been induced in conscious animals by Talbert(1899), Loucks(1934) and by Chaffee and Light(1934), Fender(1937) and Clark and Ward(1937) by use of implanted electrodes.

Loucks, Chaffee and Light, and the others, independently developed a method of stimulating the intact animal by implanting a small solenoid in the head with one electrode(diffuse) under the scalp, the other in direct contact with a desired point in the brain(or a nerve trunk). Since the solenoid is aseptically implanted, the animal quickly recovers and has no symptoms from the solenoid unless the head happens to pass into a magnetic field of a primary coil. In these circumstances the coil becomes a “secondary” and the point of the cortex to which one end has been applied becomes stimulated. In Chaffee and Light’s experiments, the rate, intensity and(within limits)the duration of the stimuli could be controlled from a distance — hence the phrase “remote control.” The reactions of the unanesthetized normal animal could thus be studied in detail.

When stimulated thus, focal seizures can be induced which follow precisely the course of clinical Jacksonian seizures, *i.e.*, the symptoms have a “march” explicable on the basis of the anatomical distribution of points in the motor area. The seizure may continue for an interval as long as 3 to 4 minutes; the animal quickly recovers from such an attack, but despite continuation of the same stimulus no further response occurs for 5 or 6 minutes; then slowly the seizure recommences, beginning as before in the thumb, spreading to the fingers and thence to the entire opposite side of the body. During the interval between responses the recently convulsed extremities show signs of motor paresis. If the seizure is strong, it may involve to a lesser extent the ipsilateral musculature which contracts in spasms synchronous with those of the opposite side. As will be pointed out below, this spread to extremities on the same side is due to ipsilateral projections from the cortex.

FLUCTUATIONS IN EXCITABILITY. The fact that the cerebral cortex becomes unresponsive for a short period after a focal epileptic seizure indicates that the excitability of the cortical elements is subject to fluctuation. Actually there appear to be several independent rhythms of excitability, *i.e.*, (i) from previous stimulation, (ii) from activity elsewhere in the cortex, and (iii) from changes in hydrogen ion concentration of adjacent tissue fluids. In their work on cortical excitability, Graham Brown and Sherrington(1912) drew attention to a phenomenon which

they designated "instability of cortical points." Thus, when a flexor response had been evoked, it proved difficult to elicit an extensor response from an adjacent point which immediately before had caused extension. They concluded on the basis of this and similar evidence that the character of the response from stimulation of a given point in the cortex depends on the previous history of that focus.

New light on this and the related problem of fluctuations of excitability of isolated points has been given by Dusser de Barenne and McCulloch(1934, 1937, 1939a), who find that, when equivalent faradic stimuli are applied to the same part of the motor area, but at various intervals, there occurs, immediately after application of the stimulus, a progressive depression of excitability of that focus which under their conditions of stimulation reached its maximum at approximately 14 secs., at which time the focus became completely inexcitable to the original stimulus("extinction"); normal threshold is reattained within 30 to 40 secs. When the cortex is exposed under a local anesthetic, the optimal interval for extinction is 4 secs.; under deep barbiturate anesthesia it may last several minutes. The duration of the phenomenon increases with the strength of stimulus, and can be readily demonstrated in all parts of the motor area. Study of cortical action potentials indicates that the first part of the period of extinction coincides with the peak of the positive voltage drift(fig. 98), and since Gasser(ch. v)has shown that the same correlation can be made in the spinal cord(a period of diminished excitability of the spinal neurons coinciding in time course with that of the positive after-potential), it is evident that changes in the excitability of the cerebral cortex are reflected by changes in resting cortical potentials. Extinction with corresponding changes in cortical potentials has also been observed in the human cortex following focal seizures(Mevers, 1941).

Further information concerning variations in cortical excitability has come from a study of the *hydrogen ion* concentration of the cortex. Brody and Dusser de Barenne(1932)noted that hyperventilation(causing alkalinity of the blood)evokes a slight but definite increase in excitability of the cerebral cortex(cats); they also reported that whereas the cortex exhibited spontaneous waves of increased excitability(Hovland and de Barenne, 1936)these waves disappeared under hyperventilation. After a period of hyperventilation, the excitability of the cortex becomes depressed for 4 to 5 minutes. Dusser de Barenne, McCulloch and Nims

(1937) have correlated the excitability cycle with the pH of the cortex and with its spontaneous electrical rhythm; thus, during hyperventilation with a rising pH (increased alkalinity) spontaneous electrical activity of the cortex (Berger rhythm) is increased in frequency, and the cortex becomes more excitable; when the pH is lowered, *e.g.*, by intravenous injection of acid, excitability becomes diminished. The phenomenon of "extinction" also appears to be associated with local changes in pH of the stimulated cortex. Thus the cortex behaves in these respects exactly like peripheral nerve, but exhibits different time relations.

Epilepsy, inhibition and excitability cycle. The practical applications of the disclosures of Dusser de Barenne and his colleagues (1937, 1938) concerning the effects of altered pH on the excitability of central neurons are far reaching, both for civilian and military neurology. Lennox (1942), in his recent résumé on epilepsy, points out that hyperventilation, which serves quickly to shift the pH of cortical neurons toward the alkaline side, precipitates epileptic seizures in susceptible individuals, both of the *petit mal* and *grand mal* type. The seizures are accompanied by changes in the electroencephalograms which, in normal subjects, are associated with an alkaline pH of cerebral blood. Gibbs, Gibbs, Lennox and Nims (1942) find that changes in the EEG caused by hyperventilation are due to a drop in the cerebral CO₂ tension and can be prevented if CO₂ is inhaled during hyperventilation.

Hyperventilation occurs as a result of emotional tension and is particularly prone to occur under conditions of low oxygen tension, *e.g.*, in aircraft, and it is now clear that many symptoms formerly attributed to low oxygen tension are in fact due to hyperventilation and the resulting shifts in pH of circulating blood. Human subjects breathing low oxygen tensions at sea-level pressure, *e.g.*, 6 per cent oxygen, hyperventilate as a result of primary anoxia and gradually lose consciousness, usually in association with symptoms of tetany. Tetany is known to be associated with low CO₂ tension (Shock and Hastings, 1935). Such individuals have been restored to consciousness by adding 5 per cent CO₂ to their oxygen mixture. All this stresses once again the importance of a clear comprehension of the factors influencing the excitability of neurons, central and peripheral.

Fluctuations in excitability of neurons of the motor area raise the question of the relation of the excitability cycle to central inhibition. This has been fully discussed in chapter v and at the present time there is no reason to believe that the period of subnormal excitability designated as "extinction" by Dusser de Barenne and McCulloch (1934) differs in any respect except time relations, from the state of subnormal excitability established for internuncial neurons of the spinal cord and other subcortical levels. Inhibition in this sense means nothing more than failure to respond when stimulated, and, as such, it adequately describes the period of subnormal excitability common to all excitable tissues. The relation of indirect inhibition to direct inhibition remains for future elucidation (ch. v).

Facilitation and Suppression. The phenomenon of facilitation and suppression requires discussion from two points of view: (i) local, and (ii) distant facilitation (and suppression).

(i)*Local*. When a weak electrical stimulus is applied to a given point on area 4 at a rate of 1 per sec. or less, the first stimulus tends to lower the threshold for subsequent stimuli. A series of inadequate stimuli may become adequate merely through repetition, and thus additional neurons become recruited through local facilitation. Once they have responded, however, the period of subnormal excitability common to all neurons develops and the phenomenon of extinction (or local suppression) results.

(ii)*Distant*. Facilitation or suppression from a distance may occur in area 4 when certain regions of the frontal lobe, as well as of the postcentral convolutions, are stimulated. Facilitation from areas 3-1-2 was first described by Graham Brown (1914), who believed that such effects were transmitted by transcortical fibres passing from areas 3-1-2 to area 4. Similar facilitation has also been established from area 6 to area 4.

Our thinking in this field has been greatly clarified through the recent studies of Dusser de Barenne and his colleagues. In a series of important papers on the organization of the cerebral cortex in monkeys and chimpanzees, Dusser de Barenne, *et al.*, have established the existence of bands of facilitation and suppression. The first suppressor band was disclosed by Marion Hines (1936), lying intermediate between areas 4 and 6 and designated by her the "strip" region (area 4s). Electrical stimulation of area 4s causes an inhibition of contraction in skeletal muscles on the opposite side (Hines), and, as de Barenne, *et al.* later disclosed a rise in threshold of area 4 and suppression of its spontaneous electrical responses. Dusser de Barenne, Garol, and McCulloch (1941b) find three other suppressor areas, namely, 8s, 2s and 12s (fig. 100, ch. XXI).

In their study of the chimpanzee cortex (1941a), these authors find similar suppressor bands and also widespread areas of facilitation (fig. 96). Thus, the arm is facilitated throughout the posterior parietal lobule and the suppressor bands correspond roughly with those established for the macaque. For details concerning the interrelations of the various areas see chapter XXI and McCulloch's chapter in Bucy (1943).

In their analysis of factors for facilitation and extinction in the nervous system Dusser de Barenne and McCulloch (1939) conclude that *facilitation* is associated with the following: (i) increase of subliminal stimulation leading to summation; (ii) negative voltage drifts (negative after-potentials) associated with decrease of threshold in neurons previously discharged; (iii) increase of pH (alkaline shift) which decreases the threshold of all neural structures in the region involved.

"*Extinction*," on the other hand, is associated with the following: (i) diminished subliminal excitation resulting in less summation; (ii) positive voltage drifts (posi-

tive after-potential) associated with increase of threshold in neurons previously discharged, and (iii) decrease in pH (acid shift) increasing the threshold of all neural structures in the region involved. Their concept of the interaction of facilitation and extinction (indirect inhibition) is portrayed in their diagram (fig. 97). Dusser de Barenne and McCulloch were careful not to identify extinction with what is now referred to as indirect inhibition, and they also insisted on designating their negative and positive after-potentials as "voltage drifts," so as not to identify them definitely with the corresponding potential changes in spinal and peripheral

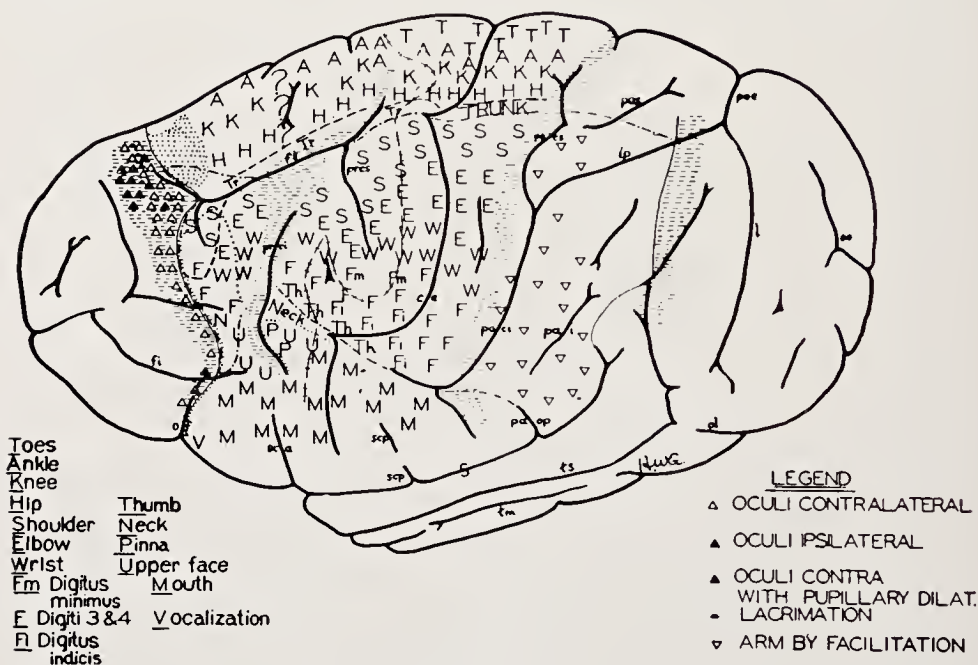


FIG. 96. The motor cortex of a chimpanzee. The primary motor area lies rostral to the central fissure, but widespread areas of facilitation as well as of suppression (see hatched bands) are clearly evident (after Dusser de Barenne, Garol and McCulloch, 1941a).

neurons. The more recent work on CO_2 tension of the cerebral cortex in relation to excitability make it apparent that the voltage drifts described by Dusser de Barenne and McCulloch can be nothing other than the algebraic summation of negative and positive after-potentials of the myriad of neurons activated when any part of the cerebral cortex is stimulated. This concept has the virtue of unifying the excitability phenomena of all units of the nervous system, and it gives a common basis for discussion of problems of excitation and inhibition in the nervous system at large. The work of Dusser de Barenne and McCulloch clearly stands as one of the important milestones of modern neurophysiology.

IPSILATERAL REPRESENTATION. Although the chief reactions to stimulation of the cerebral cortex are contralateral, both in clinically observed Jacksonian attacks and in focal seizures induced experimentally, there is always a tendency for the ipsilateral extremities to become involved,

especially in Jacksonian seizures. In connection with these ipsilateral effects, one naturally thinks of the uncrossed pyramidal tract; one may well ask whether ipsilateral movements are ever obtained as isolated reactions on stimulating the cerebral cortex. The first to record an ipsilateral reaction from the cortex were Wertheimer and Lepage(1897) who were able to evoke well marked responses in the ipsilateral hind limbs

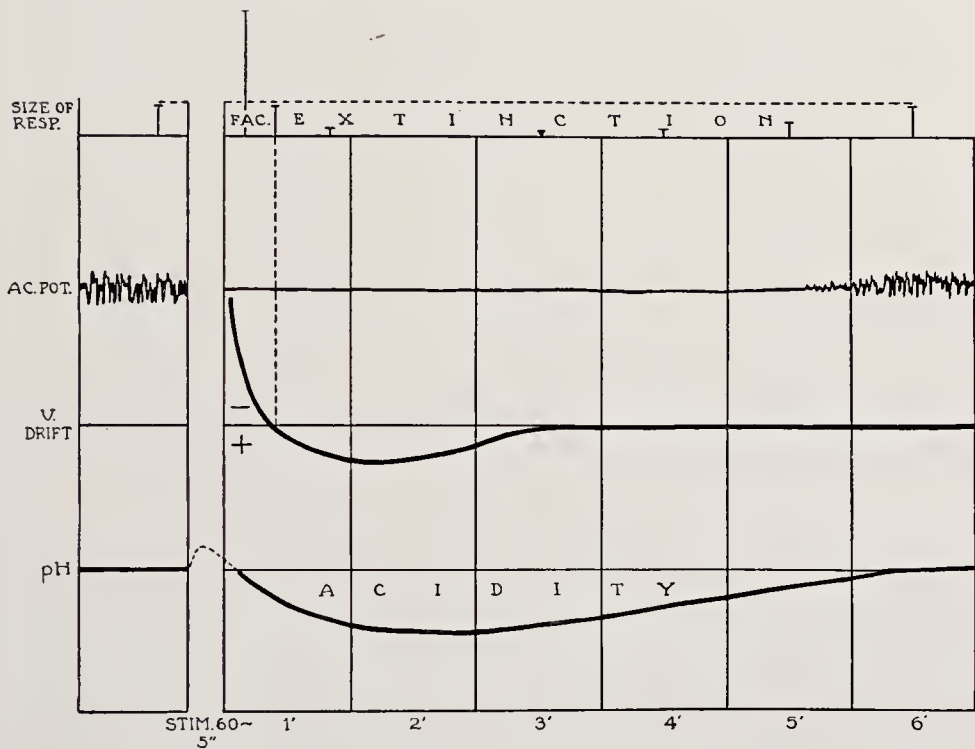


FIG. 97. Diagram correlating facilitation and extinction(subnormal excitability)with changes in electrical potentials and pH at the site of stimulation of the macaque motor area(from Dusser de Barenne and McCulloch, 1939a).

from the motor cortex of dogs; *the responses persisted after contralateral semisection of the spinal cord which proved that they were initiated from the cerebral cortex and did not arise from secondary spinal reflexes.* Gordon Holmes and Page May(1909)mention having obtained ipsilateral movements from the superior lip of the superior precentral sulcus of a macaque, and they also found that the movements persisted after lateral semisection of the opposite side of the cord.(Incidentally, Holmes and Page May record occasional chromatolytic Betz cells in the *ipsilateral* hemisphere after unilateral cord lesions.) In 1933 Bucy studied the ques-

tion of ipsilateral excitability in the cord and defined an ipsilateral area in the brain of the macaque lying in the region of the superior precentral sulcus, especially on the superior lip.

The position of the ipsilateral area in respect of the anterior margin of area 4 varies somewhat from animal to animal (Bucy and Fulton, 1933); it generally extended slightly into 4, but in most animals lay actually in the posterior part of area 6; in others it lay in the transitional cortex (strip region). The movements evoked consisted principally of flexion of the ipsilateral hind limb, being a slow movement more suggestive of a premotor than of an area 4 response. When the spinal cord was intact, the movement was associated with complex contralateral movements, but its character did not change when the spinal cord had been semi-sected; the response, moreover, was independent not only of contralateral spinal innervation, but also of contralateral cortical innervation. Furthermore when area 4a was novocainized up to the margin of the ipsilateral area the latter showed greatly enhanced excitability (1938). Wyss (1938) has also obtained ipsilateral responses with optimal, slowly-rising condenser currents. Discrete ipsilateral movements were sometimes seen in upper and lower extremities uncomplicated by contralateral movement, even though the cord was not transected. These observations indicate the existence of extensive ipsilateral innervation, probably in large measure extrapyramidal, since it persists after area 4 has been removed. Ipsilateral inhibitions have also been recorded by Tower (1936) in animals in which the pyramids have been transected. Further evidence of ipsilateral control has come through study of regional ablation.

ABLATION OF AREA 4

The effects of ablation of area 4 have been observed in detail in all representative members of the primate series including man, and as originally pointed out by Ferrier (1873) the primary symptom resulting from such a lesion is paralysis of volitional movements, especially of highly organized skilled movements; the incidence of the paralysis varies with the location of the lesion in reference to the mosaic of excitable foci in area 4. The severity of the paralysis varies in different animals, being least severe in the lower vertebrates and most conspicuous in anthropoids and man; and the monkey suffers a much less severe motor deficit than does the chimpanzee following homologous lesions. The effects of ablation will accordingly be discussed under the following headings: disturbances of (i) movement, (ii) posture, (iii) reflexes, (iv) behavioural patterns, and (v) autonomic functions. The effects of ablation of area 4 will then be compared with that of primary section of the pyramids in the medulla.

DISTURBANCES OF MOVEMENT. When area 4b is removed from monkey or chimpanzee, a profound flaccid paresis results affecting all muscles

and all movements of the entire contralateral arm. Within 1 to 3 days purposeful movements reappear at the shoulder, which allow the animal to use the extremity in rhythmic progression; later, movements of the elbow are evident and later still movements of wrist; much later (3 to 4 weeks in the monkey, 8 to 12 weeks in the chimpanzee) awkward movements of the fingers become reestablished. Movements of the proximal joints are the least disturbed by ablation of area 4, and the more complex movements of the distal joints are those most profoundly affected. Indeed, there is a close correlation between the size of a given cortical motor area representing a given muscle group and the extent of the paralysis which follows its ablation. Thus, the hip representation is relatively small, occupying only a few sq. mm., whereas the representation of the digits occupies several sq. cm. of surface (chimpanzee); the correlation may be expressed differently by saying that the movements most recently acquired in phylogenetic history, and hence those most extensively under cortical control, are the ones most seriously affected by removal of the motor area. After removal of area 4b, the chimpanzee never regains dexterity of finger movements, and such simple patterns of response as thumb-finger approximation are never regained. Foerster (1936a&c) finds the same to be true of man.

Entirely similar observations have been made on the effect of ablating the leg area on the lower extremity of the chimpanzee (Fulton and Keller, 1932); hip movements are the first to return and toe prehension the last. The paralysis which follows removal of area 4a from the *second* hemisphere is more enduring than that following its removal from the primary hemisphere, suggesting the presence of ipsilateral innervation. The reflexes of the originally paralyzed (ipsilateral) extremity are also affected by the second ablation (Fulton, 1932).

In an unpublished paper, Denny-Brown and Botterell report upon lesions of areas 4a and b of monkeys and found that individualized movements, especially of the digits, still occurred if any part of the Betz cell area was left intact, the distribution of individualized movements depending upon the part preserved; such movements disappeared if all Betz cells were destroyed. Isolated movements, therefore, depend upon the integrity of the Betz cells (Hines, 1942). Kennard (1938) has followed the development of baby monkeys in which area 4 had been removed at birth from both cerebral hemispheres. Although the animals acquired movement-patterns, finely coordinated and individualized movements of the fingers were never developed. After reaching maturity, there was little difference from the organization of these patterns seen in infancy, *i.e.*, little improvement.

FLACCIDITY AND POSTURAL DISTURBANCE. The character of the postural disturbances following lesions of area 4 has been much discussed (Fulton, 1937). Since vascular lesions of the internal capsule in human beings gen-

erally exhibit spasticity in addition to paralysis, it was assumed that lesions of area 4 likewise would cause a spastic paralysis. Actually this is not the case, and a clear distinction must be made between paralysis of volitional movement and attendant postural disturbances. The *initial* effect of ablating area 4 in monkeys and chimpanzees (Fulton and Kennard, 1934), as well as in man (Foerster, 1936b), is one of flaccidity, *i.e.*, on passive movement of the affected extremity no resistance other than that enforced by gravity is encountered. Thus in a macaque after removal of area 4 (fig. 95) the limbs exhibit no resistance whatsoever to passive manipulation during the first few days; indeed, passive resistance is much below normal in all joints during the first week. With the return of volitional movement of hip and knee, resting posture of the extremity becomes just detectable, but is less than that of the normal extremity (Fulton, 1937b). Experience with a large number of such lesions in monkeys and chimpanzees has indicated that the proximal joints remain relatively flaccid indefinitely; the wrist and digits, however, pass through a phase of *digital spasticity* between the third and fifth week after the ablation (Denny-Brown and Botterell). The digits become strongly flexed ("clawed") and the wrist exhibits increased resistance to passive movements; but the phase of digital spasticity is transient both in the monkey and chimpanzee, and after it passes off the posture of the digits, though never quite normal, is not spastic. The flaccidity of the proximal joints is enduring.

If the lesion of area 4 is extended rostrally to include all the intermediate cortex included in Hines' (1936, 1937) strip region (area 4s), the extremities exhibit spasticity of a moderate degree in the proximal joints, as well as in the distal joints during the period of recovery of motor movement. According to Hines, this increase in resistance is enduring, though it clearly diminishes in degree with the return of volitional movement. Encroachment upon the posterior part of area 6 in the chimpanzee invariably leads to increased resistance to passive movements, especially of the upper extremities (Fulton and Kennard, 1934).

REFLEX CHANGES. During the first days following ablation, all reflexes in the affected extremities are depressed; in chimpanzee and man it is quite impossible to obtain even a knee jerk. Despite the flaccidity, however, the deep reflexes generally become moderately increased in all parts of the extremity. The other reflex changes differ in different species: thus, a true sign of Babinski (up-going of the great toe on stroking the

plantar surface) is present only in anthropoids and man. In monkeys and baboons, the phenomenon of "monoplegic flexion" occurs in the affected extremity which is the equivalent of the Babinski response in higher forms.

In man and chimpanzee the sign of Babinski is pathognomonic of a lesion of the pyramidal tract. The sign of Chaddock (up-going of the toe similar to the Babinski sign), which is evoked on stimulation of the skin on the lateral side of the foot, merely represents an extension of the reflexogenous zone inducing the generalized withdrawal reflex of which the Babinski response is a part. The responses of Schäfer, Gordon and Oppenheim, used in Clinical Neurology, also fall into the category of withdrawal responses to nociceptive stimuli. There are no other significant reflex disturbances in the lower extremities following lesions restricted to area 4. When the strip region is included in the lesion, deep reflexes become uniformly exaggerated and there tends to be spreading of myotatic reflexes from one digit to the next. The pathological reflexes following lesions of area 4b in the chimpanzee have not yet been fully studied (see ch. XXI).

Atrophy. One of the conspicuous late effects of lesions restricted to area 4, especially in the chimpanzee, is a profound atrophy affecting more particularly the distal muscles. In one chimpanzee 9 months after a lesion of area 4, the muscles on the affected side weighed less than a third of the corresponding muscles on the normal side (Fulton, 1936a). In another the atrophy was more than 50 per cent. Atrophies of this character have not been observed following lesions of any other cortical area, being notably absent after ablation of the postcentral convolution and other parts of the parietal lobe. It is probable that the corresponding atrophies with sensory disturbance after "postcentral lesions" (Head and Holmes, 1911) are due to encroachment of the lesion upon area 4 (*i.e.*, upon the anterior wall of the central sulcus). Atrophy from such lesions is evidently the result of disuse.

BEHAVIOURAL DISTURBANCES. In approaching the problem of the relation of the cortex to higher adaptive behaviour of primates, one of the first questions to be considered is whether or not removal of the motor area influences the capacity to "learn" new skilled manoeuvres, or to retain those which have been previously acquired. Krasnogorski (1909, 1913) in a series of studies carried out in Pavlov's Laboratory found that conditioned reflexes to proprioceptive stimulation were permanently

abolished in dogs after removal of the sigmoid gyrus. Corresponding study of conditioned reactions has not yet been carried out in monkeys, but the problem-box technique has given relevant information (Jacobsen, 1931, 1934).

Animals were trained on a series of problem-boxes, solution of which required the establishment of an easily recognized highly coördinated pattern of skilled movement. Once the animals had learned how to open the box, they were given a rest period for one to two months. Retention tests were carried out immediately before operation, to prove that they had not forgotten the solution. Area 4 was then completely removed. Tests for the retention of the previously established skilled movements were made at weekly intervals after operation, using only one half the series of problem-boxes. Within the first two or three months after operation, first the coarser and later the finer adaptive movements of the arms and hands returned, and the animal generally approached its former level of proficiency. At that time it was tested with a second half of the problem-boxes with which it had had no experience subsequent to operation. The same procedure was followed when area 4 for the upper extremities was removed from the second hemisphere.

This same procedure, originally followed in monkeys, has now been repeated in chimpanzees and the results which are in general the same may be summarized as follows (Jacobsen, 1934): Following virtually complete bilateral destruction of the area 4b, there was profound paralysis, from which the animal gradually recovered in two to three weeks, though finer movements of the fingers were never reacquired. Immediately after operation opening of the boxes was accomplished with difficulty. Although the animal showed serious incoördination there was clear evidence that it "knew" what to do but encountered difficulty in executing the necessary movement. Orientation toward the problem situation was excellent at all times after the operation. In the case of the chimpanzee the foot was used to assist in manipulating the levers of the box during the period of weakness of the arms; corresponding adaptations were less frequently seen in the monkey.

Tested on the second half of the problems, four to six weeks after operation, there was no impairment of the responses, as judged by the time required, and by the general methods employed for opening the boxes. The results indicate that the retention of acquired habit patterns is not impaired by destruction of the motor representation of the upper extremities, although the execution of these complex manipulations may be rendered difficult for a time by virtue of motor weakness. Thus far there has been no evidence in monkeys or in chimpanzees suggesting

the existence of dominance of one hemisphere over the other. In discussing these results Jacobsen observes(1934):

“The experiments confirm the findings of Rothmann and Lashley that in the monkey the intactness of the pyramidal system is not essential to formation and retention of habits, and indicate that the extent of recovery of finely adapted responses of the digits may approach the level of the normal animal. In the chimpanzee the evidence indicates that the intactness of area 4 is not essential to the retention of motor habits studied in the present experiments. In contrast to the monkey, recovery of the use of the digits seemed to be very incomplete and it was necessary for the animal to substitute gross movements or other motor mechanisms.

“It is apparent that in the absence of area 4, non-pyramidal mechanisms were capable of functioning in the activation of lower centers without opportunity for relearning the specific pattern of movements required for the solution of the problems, but that removal of the motor areas for the arms rendered the execution of the movements slow and difficult. From observation of the chimpanzee in its play and exploration of the environment, it seems probable that habits which involved carefully executed wrist and finger movements and which did not permit the substitution of coarser adjustments would be permanently injured.

“The fact that behavioural deficits following the extirpation of a given area of the cerebral cortex may be compensated in these experiments more adequately in the monkey than in the chimpanzee does not justify the conclusion that the ablated region took no part in the responses of the intact organism. Indeed, a comparison of the responses of the monkey and chimpanzee several months after operation clearly indicated that the motor areas in the chimpanzee gave a smoothness to the behavioural pattern which was not recovered within the time limits of these observations, and made possible the more finely adapted responses of the digits.”

AUTONOMIC DISTURBANCES. Disturbances of autonomic function following isolated removal of area 4 or any of its parts are minimal. In chimpanzees there is generally transient increase of temperature of the monoplegic extremity for a period not exceeding a week, and thereafter the temperature is likely to be normal or slightly subnormal(Pinkston and Rioch, 1938). Stimulation of area 4 of the macaque may give marked elevation of the blood pressure and shift of the blood from the visceral into the muscular bed(Green and Hoff, 1937). Vasomotor effects are much more conspicuous following lesions of area 6 or of 6 and 4 together(ch. xxiii). Schwartz(1937)reports that lesions of area 4, unlike lesions of area 6, have little effect on the psychogalvanic reflexes of cats. Area 4 lesions do appear, however, to have some effect on the mechanism of heat regulation as evidenced by abnormal shivering responses.

Shivering. Aring(1935)studied a group of miscellaneous baboons and monkeys having various lesions of the central nervous system which he placed suddenly in a reduced environmental temperature. All animals behaved normally except for those with lesions of area 4. In this group

vigorous symmetrical shivering occurred long before there was any drop in rectal temperature. Animals with lesions elsewhere in the nervous system exhibited a slight drop in rectal temperature before shivering came on. In one animal in which the rubrospinal tract had been severed, there was no shivering in the parts of the body caudal to the lesion (cordotomy) on the ipsilateral side. This suggests that area 4 and the red nucleus are normally involved in the shivering reflex (ch. XIII).

PRIMARY SECTION OF MEDULLARY PYRAMIDS

Since area 4 gives rise to extrapyramidal, as well as to corticospinal projections, it is important to compare the effects of primary section of the pyramidal tract in the medulla with those of primary ablation of area 4. The work of Marshall and of Tower may be summarized briefly as follows: Working on cats Marshall (1934, 1936) reports, after pyramid section, disturbances of movement and gross impairment of placing and hopping reactions; he also finds (in certain positions of the body in space) an increased resistance to passive *flexion* of the limbs, and diminished resistance to passive extension. In a supine position, however, the postural resistance of the affected extremities is definitely less than normal in both flexors and extensors. In no stage of recovery was a phase of extensor spasticity observed proximally or distally (cf. Starlinger, 1897; Ranson, 1932).

Tower's (1935) independent findings in the cat confirm in most details those of Marshall; furthermore both investigators have found that when the homologue of area 4 is removed from an animal whose pyramid had been previously severed the affected extremities suffer an added increment of motor paralysis, with *considerable increase of extensor resistance*. *They state that after pyramid section in the cat "spasticity" and other signs of release are absent*. Stimulation of the motor cortex, after such a section, demonstrates the preservation within that cortex of inhibitory projections effective on tonic or clonic states present in the limbs, *i.e.*, such as are induced during ether anesthesia. Such a lesion in rhesus monkeys produces a similar though graver syndrome of deficit, *again without spasticity*. Tower and Hines (1935) found no evidence of spasticity at any stage following pyramid section in the monkey and evidence of digital spasticity was specifically sought. Botterell (unpublished) has also cut the pyramid in the monkey by the same approach, and in one animal which he studied for a period of sixteen days and then sacrificed

for Marchi studies the paresis was entirely flaccid, proximally and distally, during the postoperative interval (Fulton, 1937). Autonomic changes following pyramid section have not yet been studied, but if present they are inconspicuous. In a recent report Tower (1938) states that baby monkeys after pyramid section continue indefinitely to show infantile grasping reactions. Tower's (1940) full report on the effects of pyramidal section in monkeys concludes with the following lucidly written summary of the functions of the pyramidal tract:

"Reinterpreting the results of pyramidal lesion, the functions of the pyramidal tract are characteristically organized both in space and in time. The spatial organization derives from a relatively stable topographical relationship between loci in the cortical field of origin of the tract and loci in the motor mechanism of the spinal cord. The fineness of this topographical organization underlies the unique feature of corticospinal function: the ability to bring into action any portion of the skeletal musculature, and in all combinations. This detailed control of the skeletal musculature enables the discrete usage of the musculature, especially of the digits, and the modulation of extrapyramidal activity, which are outstanding pyramidal functions. Furthermore, by increasing the excitation in specific portions of the segmental mechanism, it may enable fragments of the stereotyped patterns of extrapyramidal activity to be brought to threshold as part reactions, detached from the frame which usually gives them usefulness. The pyramidal tract operates in a crossed relationship on the extremities, but bilaterally on the axial musculature other than abdominal.

"The functions of the pyramidal tract are not, however, covered by description, no matter how detailed, of results of stimulation in its field of origin because the organization in time is not in this manner brought out. In time, the pyramidal tract operates in two phases. On the one hand is a continuous, or tonic action in effect at all times in the waking state. On the other hand is a specifically timed increase of discharge, or phasic action, which is evoked in relation to particular situations. The tonic function contributes to the excitatory state throughout the spinal cord, supporting muscle tone, keeping thresholds low, facilitating, reinforcing, steadying and moderating whatever tonic or phasic activity may be set in train at segmental or suprasegmental levels. The delivery of this excitation is not to all parts equally, but is influenced by original preponderance, and by postural and other immediate factors. Its volume is a function of the temper of the individual and of extraneous factors of great variety, reaching its lowest level short of sleep when the animal verges on sleep either from exhaustion or from boredom.

"The phasic, or episodic function initiates movement or speeds initiation. It enters into all somatic motor activity of any complexity, to confer on the stereotyped extrapyramidal performances: adjustability in space, modifiability in the course of execution, and all the modulations of pattern which make for aim, accuracy, economy, lability and finish. More than this in the primate, this function enables the discrete usage of the musculature, and especially of the digits, which is characteristic of the order.

"Together, the tonic function provides for smooth, continuous, efficient action while the phasic function contributes, outstandingly, precision and lability to total performance. In the realm of somatic motor function both of these are unques-

tionably motor or excitor functions. Of inhibitory function as such there is no evidence.

"On the vascular system, the corticospinal system likewise exercises a continuous influence in the waking state which supports dilator tone and facilitates, reinforces and moderates reflex action. Whether this influence is excitatory of dilatation, or inhibitory of constriction is uncertain. Also whether or not there is a further phasic action has not been determined.

"Function of the pyramidal tract is thus co-extensive in time at least with the waking state, and determined in intensity by both general and specific demands of that condition. It is distributed to the entire somatic motor mechanism of the body, and to parts of the autonomic mechanism, the survey of the autonomic relationship being as yet incomplete. It is organized in complexity to match virtually the full range of activity, from simple tonic functions wherein it merely assists, to complicated performances which are primarily its responsibility. Although traditionally, the pyramidal system has been considered 'the voluntary motor pathway,' this is too sweeping. An impressive capacity for voluntary movement survives pyramid section, especially if the lesion be bilateral, forcing the issue. Conversely, some activities eliminated by pyramidal lesion, for example the contact placing reactions, must be considered, if not involuntary, at least highly automatic. By virtue of its tonic action on the spinal cord, pyramidal function must assist all somatic motor activity, if not indeed, all motor activity of the waking animal, at whatever level initiated even the spinal reflex level without regard for the voluntary or automatic quality of particular acts. As the agent of lability, however, the pyramidal tract makes a unique contribution to total performance. Together, the all-pervading, and the discriminating qualities of corticospinal action afford the cerebral cortex that influence in virtually all realms of final motor action, and that minuteness of control which determine its effectiveness as an agent of choice. In this service of choice the pyramidal tract is unquestionably the outstanding, though not the exclusive voluntary motor pathway."

PYRAMIDAL TRACT AND SPINAL MECHANISMS. Among the most important unsolved problems of physiology is the nature of the control exerted by the corticospinal system on spinal reflex mechanisms. The work of Lassek described in chapter xv indicates that more than a million fibres pass through each pyramid in man, and that less than five per cent of these originated in Betz cells. Hence, there are many small-fibred units in addition to the large, rapidly conducting fibres responsible for the primary excitatory characteristics of area 4. Adrian and Moruzzi (1939) have found the spontaneous rhythms led off from area 4 can also be picked up at the medullary pyramids. In studying the pyramidal system of the cat, Lloyd (1941b) was unable to find clearcut evidence of direct or indirect inhibitory action on the spinal cord. All fibres in his experience had excitatory effects on spinal neurons. He also disclosed that reflex antagonism exists between neurons of the dorsal and ventral halves of the cord (fig. 98), *the dorsal half being activated primarily by the*

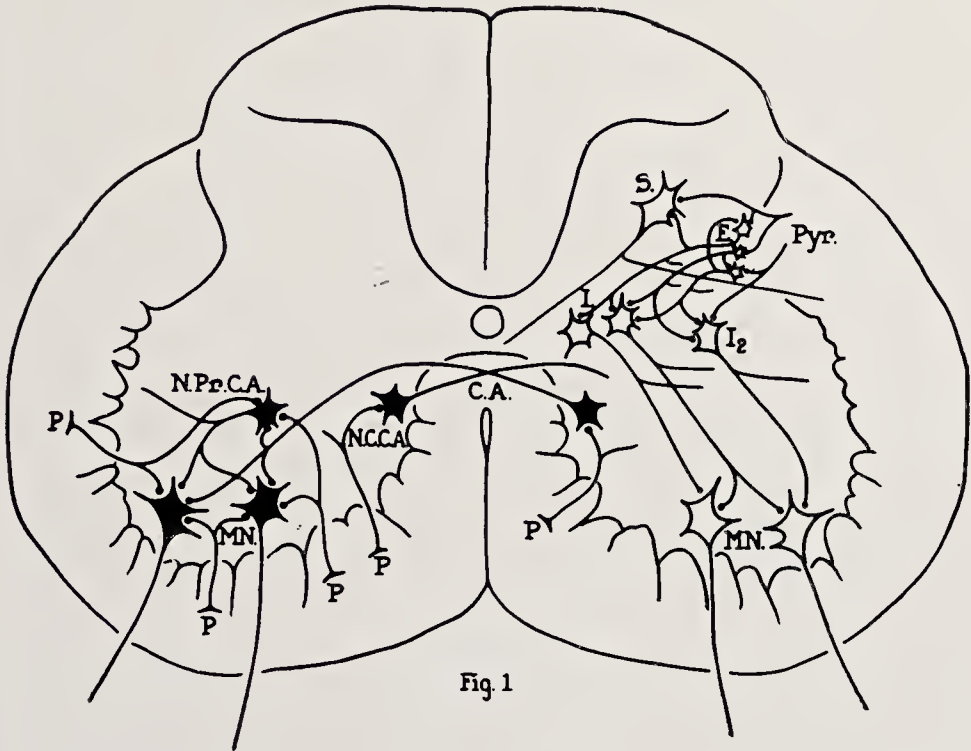


Fig. 1

FIG. 98. Diagrammatic representation of the functional organization of the lower spinal mechanism to illustrate fractionation by descending systems. The neurons *in solid black* with their processes represent that part of the spinal mechanism activated by long spinal reflex paths; the neurons *in outline*, with their processes, that part activated through the pyramidal system. The laterality of the various neurons as drawn is such that the descending activity in both cases has its origin on the left side of the body. The diagram is constructed in accordance with the findings of localization experiments employing microelectrodes placed at will within the grey substance, and from information gained by observing the interaction between descending systems and local reflex systems. No attempt has been made to depict the structures mediating primary inhibition, for there is at the present time no satisfactory picture of the anatomical structure underlying the phenomenon. To avoid excessive complexity, primary afferent collaterals of the segmental system are omitted. These supply motor neurons (M.N.) directly to form two-neuron arcs, the intermediate gray nucleus of Cajal (I), and presumably other regions to form multineuronal arcs. For example, excitatory activity reaching I from the pyramidal system facilitates three-neuron-arc discharges at the internuncial level. C.A., anterior commissure; E, small cells of the external basilar region of the dorsal horn; I, intermediate grey nucleus of Cajal; I₂, other neurons of the intermediate region; M.N., motor neurons; N.C.C.A., nucleus of the anterior commissure; N.Pr.C.A., interneurons of the ventral horn; P, propriospinal fibres of the long spinal reflex system; Pyr., fibres of the pyramidal tract; S, solitary cells of the dorsal horn (David P.C. Lloyd, unpublished).

flexor reflex and pyramidal system. Approximately 85 per cent of pyramidal tract fibres of the cat terminate upon dorsal internuncial neurons, (E. C. Hoff, 1932; see also Peele, 1942). The ventral half of the cord is activated, on the other hand, by vestibulospinal, reticulospinal, long interspinal neurons and receptors of the stretch reflex. There is thus antagonism between the dorsal half of the spinal cord controlled by the pyramidal system, and the ventral half, which is controlled primarily by extrapyramidal projections from medulla and reticular formation. This antagonism between the dorsal and ventral halves of the spinal cord may provide some of the inhibition manifest in reciprocal innervation provided only that the dendrites and axon collaterals of the cells in the two regions are appropriately related to one another in space, for Barron and Matthews(1935, 1938) have shown how potentials in an active area in the central grey matter may, by electrotonic spread, induce anelectrotonic blocks on axons via their collaterals.

SUMMARY

The classical motor area of the higher primates arises in the depths of the central sulcus and extends for a variable distance rostrally on the precentral convolution. Although many parts of the cerebral cortex are responsive to stimulation, area 4 is the most excitable, and when removed finer volitional movements became entirely abolished.

On stimulation of area 4, especially if carried out with optimal slowly-rising currents, isolated movements arising from small muscle groups can readily be elicited. Such a mosaic of foci cannot be demonstrated elsewhere in the cortex. Evidence of well developed *ipsilateral* representation is found in the region of the superior precentral sulcus. Less discrete isolated movements can also be obtained by facilitation in regions adjacent to the motor area(*e.g.*, areas 6 and 3-1-2; ch. XXI), but such responses depend upon the integrity of the motor area, disappearing completely when it is removed or when the transcortical fibre connections are severed(ch. XXI). The excitable properties of area 4 depend largely, if not entirely, upon the integrity of the Betz cells in the vth layer, isolated movements disappearing when these are destroyed by thermocoagulation or by retrograde degeneration; if the Betz cells are undeveloped(as in infants), isolated movements similarly cannot be obtained.

The excitability of area 4 is subject to cyclic fluctuations. Thus, after

maximal stimulation in the macaque excitability dwindles and after about 14 secs. becomes temporarily abolished ("extinction"). There are also longer cycles of spontaneous fluctuation which depend upon changes in the pH of the blood. Within certain limits any agent or condition that increases the pH augments the excitability of area 4; conversely, any agent or condition which depresses the pH (*e.g.*, accumulation of acid metabolites) depresses the excitability of area 4. Fluctuations in excitability following stimulation are correlated with the negative (facilitation) and positive (inhibition) after-potentials. Excitability is also diminished by activation of the suppressor areas (fig. 96).

Ablation of area 4 causes an enduring paralysis of isolated movements, especially those of the distal joints. Gross movements of proximal joints, *e.g.*, progression movements, are less affected. Following lesions of the posterior three-quarters of area 4 in the macaque and chimpanzee, the paralysis is flaccid in character in the proximal joints, but the fingers and wrists pass through a stage of moderate spasticity with increased deep reflexes, clonus, etc., during the third to the fifth week after the ablation. If the intermediate cortex (strip region) is also included in the lesion, mild spasticity may develop in the proximal joints. Enduring spasticity in the chimpanzee is seen only when areas 4 and 6 have been removed (ch. XXI).

Isolated section of the pyramidal tract in the medulla gives rise to pure paralysis of isolated movements without trace of any of the spastic release manifestations just mentioned (Tower). From this it is concluded that interruption of the pyramidal tract *per se* gives pure paralysis, and that such spastic manifestations as occur after lesions of area 4 are due to simultaneous interruption of extrapyramidal projections.

Ablation of area 4 also causes an exaggerated shivering response and transient vasomotor changes. No disturbances of conscious sensibility can be attributed to lesions of area 4.

XXI

CEREBRAL CORTEX: EXTRAPYRAMIDAL AND INTRACORTICAL PROJECTIONS

HISTORICAL NOTE

Following discovery of the excitability of the cerebral cortex the relation of the cerebrum to subcortical systems such as the striatum and cerebellum was considered, and more recently the influence of the cerebral cortex upon the red nucleus, substantia nigra and hypothalamus has been much under discussion. A. W. Campbell(1905) was the first to draw attention to the fact that lying just rostral to the motor area is a large region histologically similar to area 4 which is obviously motor in function(ch. xv). He designated this portion of the frontal lobe the "intermediate precentral area." Brodmann recognized the homologous area in monkeys and designated it "area 6" in his numerical scheme. Latterly it has been appropriately termed "the premotor area." Its functions are obviously closely related to those of area 4 and clinical writers have often grouped them together as a single entity. Anatomical and physiological evidence, however, necessitate their functional separation.

Adie and Critchley(1927) noted that lesions of area 6 in man give rise to the phenomenon of forced grasping, and in 1932 Richter and Hines found that isolated removal of this area, and of no other part of the cortex, caused forced grasping in macaques. Fulton, Jacobsen and Kennard(1932) extended the observation to baboons and chimpanzees, and later it was observed in chimpanzees that isolated ablation of area 6, not only caused forced grasping but also a conspicuous disturbance of skilled movements(Jacobsen, 1934), transient spasticity and vasomotor aberrations(Kennard and Fulton, 1933); spasticity, although often observed, was never enduring unless area 4 was also destroyed.

The Vogts(1919) reported upon the excitability of area 6 and of other extrapyramidal projection areas, finding that stimulation of area 6 gave slow and complex movements after area 4 had been destroyed. Foerster confirmed this finding in man, observing, as had the Vogts, that regions in the parietal and temporal lobes were also responsive to strong galvanic stimulation. Fresh meaning was thus given to the motor projections which take origin in these regions.

Too little is known as yet concerning the spatial organization of the extrapyramidal projections from the cortex. Those from the precentral gyrus(areas 4 and 6) may be regarded as a unit since they project to the same subcortical areas, but within this region there is nevertheless a prevalence of representation; *i.e.*, the extrapyramidal projections from posterior 4 appear to affect the distal musculature, those from the strip

region govern the proximal extensors, and those from the anterior area 6 preside over the flexor muscle groups. In the parietal lobe the organization appears to be more similar to that of the corticospinal neurons in the motor area, the superior part controlling the lower extremities, the more lateral part the upper extremities and face. In discussing the functions of the extrapyramidal projections therefore, responsiveness to stimulation will first be described and then the effects of ablation, where these are known.

STIMULATION OF EXTRAPYRAMIDAL AREAS

In Grünbaum and Sherrington's(1901)and Leyton[Grünbaum]and Sherrington's(1917)experiments excitability for ordinary strengths of faradic current was restricted anatomically to the posterior part of the frontal lobe(except for the eye fields in the frontal and occipital regions), but they pointed out that the anterior limit of excitability in the frontal lobe was variable and through facilitation it could be extended well to the anterior part of Campbell's intermediate precentral zone. They also emphasized, as have all others who have stimulated area 6, that movements from this area tend to be more complex than the isolated movements evoked from area 4. In the case of areas 6 and 3-1-2, a distinction must, however, be made between their excitability before and after removal of area 4(or severance of pyramidal tract), for the responsiveness of all these areas to weak stimuli is dependent upon the integrity of the corticospinal pathway.

A. Efferent motor responses

AREA 6. For purposes of description of excitable zones, it is desirable to use the subdivision of area 6 adopted by the Vogts, even though certain of their partitions are of doubtful functional significance. The Vogts(1919)recognize two primary regions(fig. 99):(i)an upper part, area 6a, immediately rostral to leg and arm areas and coinciding with the premotor area proper; this they divided on the basis of cellularity of the vth layer into two parts, area 6a α and 6a β (fig. 99);(ii)a lower part, inferior and rostral to area 4, in which three subdivisions are recognized — area 6a α , 6b α and 6b β (fig. 99). The relative positions of these areas are slightly different in the human brain, but each area has been homologized for man by Foerster(see fig. 95). The somatic motor responses from the principal divisions are as follows.

Area 6aα (upper part). Faradic stimulation of this, the posterior part of the premotor area, gives rise contralaterally to (i) isolated movements of individual muscles — the *Spezialbewegungen* of the Vogts — similar in character to those obtained from area 4, but *always less discrete*, and (ii) secondary sustained and more highly organized movements, the *Einstellungsbewegungen* of the Vogts. The latent period of response from area 6aα is greater than that from area 4 and the tendency toward after-discharge more marked. By making a superficial incision of the cortex between area 6aα and area 4, the movements of individual muscles

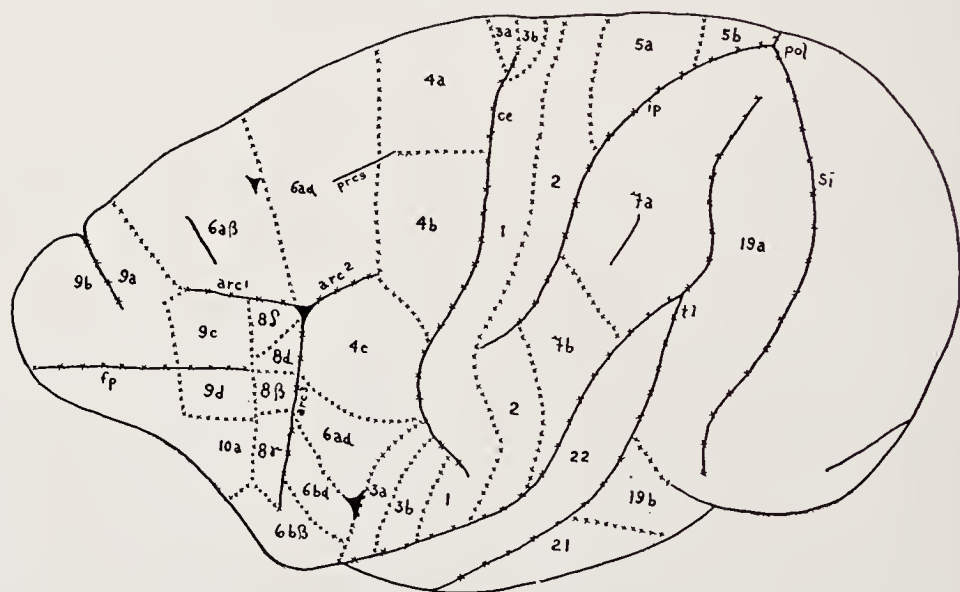


FIG. 99. The Vogts' (1919) diagram of principal cytoarchitectural areas in brain of cercopithecine monkey. Subdivisions of area 6 and of area 8 are shown. The Vogts retain Brodmann's numerical designations, but, as indicated in the diagram, they subdivide many of his fields. A similar subdivision of face area of chimpanzees has been made by Walker and Green (1938).

elicitable from area 6aα are abolished, but certain of the sustained movements remain. Furthermore, if area 6aα is undercut prior to slitting the cortex between 6aα and 4, the sustained movements tend largely to disappear while the isolated movements remain (confirmed by Bucy, 1933a). It follows from this that the isolated movements evoked from 6aα on faradic stimulation are mediated via the motor area, and that the more sustained movements from area 6aα are mediated through extrapyramidal pathways from area 6aα via the substantia nigra, reticular substance, cerebellum, etc. Many sustained movements remain after complete degeneration of the projection fibres from area 4.

Ipsilateral area. From the posterior part of area 6aα a specific ipsilateral area was found by Bucy (1933a). In the majority of macaques it lay on the superior lip of the superior precentral sulcus and extends over an area 6–7 mm. long and 3–4 mm. wide, trespassing slightly upon the anterior margin of area 4 (see ch. xx). Such a region has not been observed in man.

Area 6aβ. This, the rostral part of the premotor area, yields somewhat similar

responses to those of area 6a α , but a higher threshold. The region, moreover, is scarcely distinguishable histologically from area 6a α , the motor cells of the vth layer being somewhat less numerous. From this region isolated movements are seldom if ever obtained, the primary response being a complex sustained movement depending in part on area 4, and rhythmic and stereotyped movements which are quite independent of the motor area and are abolished by undercutting the cortex (Bucy, 1933b). In accordance with Beevor and Horsley (1890a) the area yields, in addition to stereotyped movements of the extremity, characteristic *adversive movements* of the head and trunk, *i.e.*, turning of head and eyes to the opposite side, with rotation of the trunk in the same direction. For this reason Foerster (1936b) terms it the "frontal adverse" field. Epileptiform seizures from this area begin with head-turning and deviation of eyes and body to the opposite side. Similar adverse movements have been obtained from this region in the macaque (Smith, 1936) even after ablation of area 4 or after medullary section of the pyramids. Penfield and Boldrey (1937) have not seen adverse responses from area 6a β in man. Adversive movements are also elicitable from area 8 which lies just below 6a β . In view of the historical similarity between area 8 and the anterior margin of area 6a β Hines (1937) has suggested that this anterior strip is in reality a part of area 8.

Wyss and Obrador (1937) have studied the excitable properties of area 6a in the macaque, finding that the optimal current pulse probably has a rising phase between 10 and 30 msec. in duration, and the optimal rate of stimulation is about 4 per sec. The general characteristics of the responses were similar to those just described: *i.e.*, there were no isolated movements, and the latency of response and the after discharge were both prolonged. Certain recent work suggests that the complex movements described by the Vogts, Bucy and others after removal of area 4 may be due in part to the smaller and sparsely scattered Betz cells found in the intermediate zone. In Denny-Brown's experience, the only consistent movements following ablation of area 4 plus the strip region were stereotyped flexion and extension movements of the fore and hind limbs; and from the more anterior parts of area 6 adverse movements of head and eyes.

Area 6a α (lower part). From this region individual movements of face, mandible and tongue can be obtained which are similar to but less isolated than those elicited from area 4c, as well as secondary postural movements of these muscle groups. Undercutting destroys the latter (Walker and Green, 1938). For early literature see Semon and Horsley (1890).

Area 6ba. In man this small region lying rostral to motor representation of face, tongue, glottis, etc., tends on stimulation to give rise to sustained, and sometimes long-continued movements, rhythmic and coördinated in character, of lips, tongue, mandible, pharynx and larynx, *i.e.*, chewing, licking, salivation, swallowing, mastication, croaking, grunting accompanied by noises resembling the smacking of the lips. Penfield and Boldrey (1937) have obtained outspoken vocalization from this area in man (ch. xx). The chewing, swallowing, etc., were also seen in cats, apes and in monkeys. In the spider monkey persistent chewing and swallowing movements occurred associated with active salivation from stimulation of this area; the perseverating character of their movements was striking, *i.e.*, once started they may continue for an almost indefinite period of time. The Vogts (1919) observed that isolation of this area through incision of the cortex surrounding it does not alter the responses, and removal of areas 4c and 6b β is similarly without effect, but the movements can be inhibited by stimulating area 8 γ .

Area 6b β . Weak stimulation in this region causes slowing, and a stronger stimu-

lus, probably from spread to area 13 on the orbital surface(ch. xxii), complete cessation of respiratory movements, whether applied in the phase of inspiration or expiration(Smith, 1938). Occasionally also rhythmic movements of mastication are obtained in this region. Slowing and cessation of respiration has been induced by Bucy and Case(1936)by stimulation of area 6b of man. Disturbances of breathing movements, moreover, are well known as "aura" preceding epileptiform seizures.

Area 13. Lying on the orbital surface of the frontal lobe is a discrete area which on stimulation causes cessation of respiration; it has come to be recognized as the primary respiratory center of the cerebral cortex(Bailey and Bremer, 1938; Bailey and Sweet, 1940, ch. xxii).

EYE FIELDS. The frontal eye fields, which were first accurately defined in monkey by Beever and Horsley(1890b)and in chimpanzees by Grünbaum and Sherrington(1901), occupy a relatively small area of cortex lying just rostral to the motor face area(area 4c and area 6b); in the monkey they are found within the rostral crotch and in the depths of the arcuate sulcus(fig. 99); in man and chimpanzee it forms the posterior part of the second frontal convolution(fig. 95). In the Vogt and Foerster maps of monkey and man frontal eye fields are designated area $8\alpha\beta\delta$. The occipital eye fields are in areas 17 and 18.

Area $8\alpha\beta\delta$. Grünbaum and Sherrington(1902a, 1903)pointed out that faradic stimulation under light ether caused conjugate movements of the eyes to the opposite side. In the chimpanzee, gorilla and orang, Leyton and Sherrington(1917) observed that the eyelid could be opened by stimulation over a fairly wide region corresponding with area $8\alpha\beta\delta$ of the Vogts but extending into the third frontal convolution(area 8 γ and area 9); closure of the eyes, especially the opposite one, was also obtained regularly in certain specimens from a point further lateral on the hemisphere. Conjugate movement of the eyes to the opposite side was commonly observed from the second frontal convolution in the region corresponding with area $8\alpha\beta\delta$. Opening of the eyelids is generally associated with conjugate movements of the eyeballs. In Leyton and Sherrington's experience the movements are nearly always lateral. Dilatation of the pupils was occasionally induced from area $8\alpha\beta\delta$. Bender and Fulton(1938)have studied the responses of area 8 in a chimpanzee and, using the Wyss technique, have confirmed all of Leyton and Sherrington's observations; the frontal eye field, however, is slightly more circumscribed than is indicated in Leyton and Sherrington's map. Similar results are recorded by Hines(1940)and W. K. Smith(see Bucy, 1943).

Foerster(1936b)and others have stimulated area $8\alpha\beta\delta$ in man under local anesthesia. Strong conjugate deviation of the eyes to the opposite side followed stimulation; in a few cases upward movements, and in one case downward. The head does not participate in the reaction and there are no visual hallucinations associated with it as with occipital lobe stimulation. Epileptiform attacks have also been induced in man through faradic stimulation, a seizure beginning with clonic lateral movements of the eyeballs; in a few cases the seizure was restricted to the extraocular muscles, but in general it spread to the muscles controlled by area 6a β (movement of the head to the opposite side), or to the face area. Spontaneous focal

seizures beginning with the eye muscles have frequently been recorded, and in such cases lesions have been found in the frontal eye field.

Area 8γ. The most lateral parts of the frontal eye fields occupying the posterior end of the third frontal convolution in man have been designated area 8γ by the Vogts. According to these writers stimulation of area 8γ inhibits rhythmic movements induced by stimulation of area 6b. Thus if mastication has been induced, stimulation of area 8γ will inhibit the masticatory activity. Walker and Green (1938) were able to obtain similar effects in the macaque.

Areas 17-19. The occipital eye fields were discovered by Schäfer (1888b) and further studied by Grünbaum and Sherrington (1901). Eye movements from this region consist of conjugate deviation of the eyes to the side opposite the stimulus and occasionally opening of the eyes. This field is more fickle and responses are sometimes more difficult to demonstrate than in the frontal fields. In man stimulation of this region causes visual hallucinations: sparks, stars, intense light, etc.; they are referred to central vision when the occipital pole is stimulated and to peripheral vision if the lateral parts of the hemisphere are excited. Stimulation of areas 18 and 19 cause highly organized visual images. Foerster has not been able to evoke eye movement from area 17 in man, but he obtains them readily from area 19.

Areas 9-10-11-12. These areas will be discussed in ch. xxii (see fig. 102).

PARIETAL AND TEMPORAL CONVOLUTIONS — *Areas 3-1-2 and 5.* Graham Brown has obtained facilitation responses for excitable points in area 4, by stimulation of areas 3-1-2, but primary movements were rarely seen. This general result has been confirmed by the Vogts (1919) in the cercopitheque monkey, but they insist that with strong stimuli (10 to 20 times the intensity required for area 4) there are sometimes discrete primary movements. Hines (1940) and Dusser de Barenne, Garol and McCulloch (1941) agree that the postcentral convolution of the chimpanzee is excitable, but the later authors insist that previous facilitation is required to evoke a response (fig. 96). Foerster in a detailed study of the excitability of the human cerebral cortex under local anesthesia finds, as with area 6, that stimulation of areas 3-1-2 and 5 gives rise to discrete and complex movements, the former depending upon the integrity of area 4. Penfield and Boldrey also record isolated movements from areas 3-1-2 of man, but not from area 5. Accurately localized sensory impressions are also evoked from this region as was originally disclosed by Cushing (1909).

Area 7. No motor effects occur on stimulation except through facilitation (fig. 96), but auditory and visual hallucinations are prone to occur with conscious human subjects (Penfield and Boldrey).

Area 22. Stimulation of area 22, especially in its posterior part, gives rise to vertigo in man, and Foerster and Penfield and Boldrey find that pronounced motor effects are also obtained similar to those induced from areas 3-1-2.

It is scarcely an exaggeration to state that the human brain has been as thoroughly studied from the point of view of electrical excitability as that of the anthropoid ape. Penfield and Boldrey (1937) have observed responses to stimulation in some 150 human beings and Foerster has stimulated nearly 200 subjects, exploring every accessible area of the cortex faradically and galvanically; and he and Penfield have correlated

their findings with the known cytoarchitectural fields in man. Foerster (1936a) concluded his lectures on the motor areas of man as follows:

"Let me review briefly the effects of stimulating the different motor areas: 4, 6a α , 6a β , 8, 3-1-2, 5a, 5b and 22. We have seen that the areas 4, 6a β and 3-1-2 react with single innervations of single muscle groups, of a single muscle or even a part of a single muscle. Area 8 reacts with isolated movements of the eyes. The isolated effects obtained by stimulation of the areas 6a α and 3-1-2 are due to physiological transmission of the stimulation to area 4, *i.e.*, they depend upon the integrity of the area 4 and its motor pathway, the pyramidal tract. So we can say that the area 4, the area pyramidalis, is the specific area for isolated innervations.*

"When area 4 or the pyramidal tract is destroyed, all the other areas 6a β , 5a, 5b, 22 (and the areas 6a α and 3-1-2 also) react with complex movements: eyes, head and trunk are turned to the opposite side and the contralateral extremities achieve typical complex synergies, the flexor or the extensor synergy. I call collectively all these cortical fields extrapyramidal areas. In figure 95 the pyramidal area is represented by the black area, and the extrapyramidal areas are hatched.

"Both groups, the pyramidal area, and the extrapyramidal areas, coöperate when voluntary movements are performed. If area 4, the area for isolated innervations is destroyed, the pyramidal tract is interrupted, isolated movements of single segments of the extremities can no longer be performed. But voluntary mobility is by no means abolished completely. The movements which are performed under these circumstances are distinct and typical synergies:

"(1) The flexor synergy of the arm, which is observed in each severe case of spastic hemiplegia or tetraplegia, is composed of adduction of the upper arm, flexion of the forearm, pronation of the hand and flexion or extension of the fingers. These figures equally demonstrate the flexor synergy of the superior extremity.

"(2) The extensor synergy of the arm is composed of adduction of the upper arm, extension of the forearm, pronation of the hand and flexions, seldom extension, of the fingers.

"(3) The flexor synergy is combined flexion and adduction of the femur, flexion of the tibia, dorsiflexion and supination of the foot and dorsiflexion of the toes. The extensor synergy of the leg is composed of extension and adduction of the femur and flexion of the tibia and plantar flexion of the foot; the toes are flexed or extended.

"Furthermore, when in cases of destruction of the pyramidal tract a voluntary movement is to be achieved, the flexor synergy of the arm often is combined with the flexor synergy of the leg, and vice versa the extensor synergy of the arm with that of the leg. This can be well observed in hemiplegia. When the leg is flexed the arm shows the flexor synergy also and when the leg is extended the arm is extended also. In cases of spastic tetraplegia due to complete bilateral destruction of the entire pyramidal tract, all four extremities act together, whichever of the latter is moved voluntarily they are all flexed, if one single segment of one leg, for example, one foot is to be flexed, or one arm is to be flexed. They are all extended if one single segment of one arm, for example, the forearm is to be ex-

* These lectures unfortunately were never published in detail. The above quotation is from a stenographic report of the Lecture which Prof. Foerster kindly allowed me to quote. The material was again summarized in Foerster's Hughlings Jackson Lecture (1936a).

tended. These synergies performed when a single movement is to be achieved voluntarily, reveal the specific functions of the extrapyramidal motor areas."

EXCITABILITY OF CORTEX AFTER SECTION OF MEDULLARY PYRAMID. Much more satisfactory from the point of view of analysis of the extrapyramidal projections are the results of stimulating the various areas following acute or chronic section of the pyramids in the medulla. Marshall (1935) and Tower (1937) have described the effects in the cat, and Tower (1940) has recently studied the problem in monkeys. As with Denny-Brown's stimulation following complete removal of area 4 and strip region, one can obtain stereotyped synergies, generally slow in character, from the opposite extremities similar to those just described by Foerster. More conspicuous, however, are the prompt inhibitions of resting postures, particularly the grasp, which are readily obtained from areas 4 and 6. Tower is therefore inclined to stress the inhibitory function of the extrapyramidal projections, a point of view which is thoroughly supported by the ablation studies.

B. Responses of other cortical areas

Activity in one area of the cerebral cortex generally affects other regions, and as further knowledge is gained of these remote actions it be-

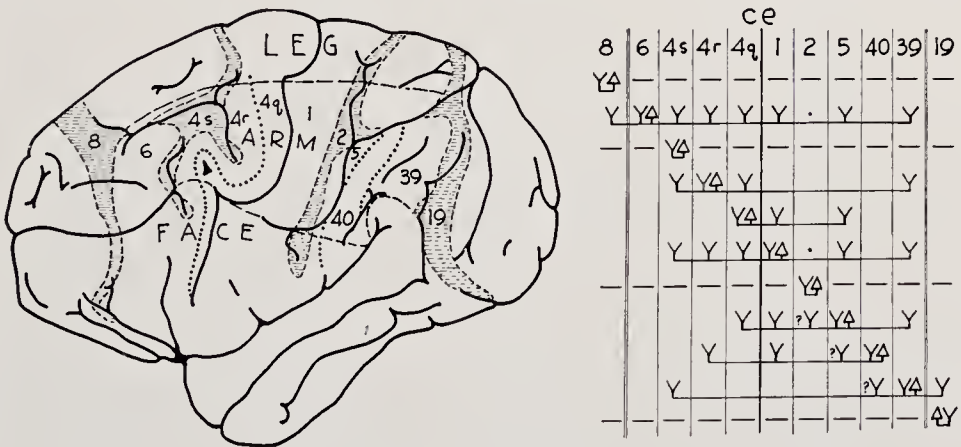


FIG. 100. Diagram showing primary cytoarchitectural areas of chimpanzee sensori-motor cortex with indication of the four suppressor bands, *i.e.*, areas 8s, 4s, 2s and 19s, as elucidated by the strychnine method. Areas 6, 4, 3, 1, 5 and 7 constitute the sensori motor cortex with area 4 as the primary motor area. At the right is the "firing" diagram: Y, activation; —, suppression; Δ, area strychninized. Areas 8s and 19s are immediately adjacent to areas of thalamocortical projection and are not, strictly speaking, to be regarded as sensory cortex (from McCulloch in Bucy, *The precentral motor cortex*, Chicago, 1943, by kind permission).

comes possible to understand the functional organization of the cerebral cortex as a whole. We owe to the strychnine method of Dusser de Barenne and to the electroencephalographic studies inaugurated by Berger(1923) and extended by Adrian and Matthews(1934) and many others the principal advances in this new and important branch of neurophysiology. Accepting the subdivisions in figure 99, and recognizing the four suppressor areas of Dusser de Barenne(fig. 100) it becomes possible to develop a chart of functional organization which relates virtually all the principal areas to one another in the homolateral as well as in the contralateral hemispheres. In his lucid chapter in Bucy's *Precentral motor cortex* McCulloch summarizes the inter-areal relations of the chimpanzee as follows(fig. 100):

HOMOLATERAL CONNECTIONS. The inter-areal connections by cortico-cortical axons can best be divided into those which are afferent to and those which are efferent from the area in question. The commissural connections are most commonly symmetrical, but the exceptions are important and therefore must also be specified. Area 4 of the chimpanzee has been subdivided into two parts, 4q and 4r.

Area 4q receives cortico-cortical impulses from areas 4r, 6a, 1, 5, and in the leg field from 7. It sends impulses to areas 1 and 5.

Area 4r receives impulses from areas 6 and 1, and in the arm from what is here called area 40. It sends impulses to areas 4s, 4q and what is here called area 39.

Area 4s receives impulses from area 6, 4r, 1 and 39, but sends only to area 32. The last confirms anatomical finding of a tract running from 4s into the vicinity of the sulcus calloso-marginalis described by Walker(Bucy, 1943).

Area 6 has so far yielded no cortico-cortical afferents. Area 6, for leg and arm, sends impulses to leg and arm subdivision of areas 4s, 4r, 4q, 1, 5; also into 39 from the arm and into the superior parietal lobule from the leg subdivision. Area 6 for face probably sends impulses to the face subdivision of the parietal lobe.

Area 8. No cortico-cortical afferents have been found, and no cortical efferents except to areas 32 and 18.

Area 47. No cortico-cortical afferents have been established. Its cortical efferent system runs, via the fasciculus uncinatus, to area 38, which is the temporo-polar area.

Area 24. No cortico-cortical afferents have so far been disclosed, but they have not been sought exhaustively. Its cortico-cortical efferent fibres run into areas 31 and 32.

Areas 31 and 32 receive impulses from areas 19, 2, 4s, 8 and 24 — *i.e.*, from all suppressor areas hitherto found.

COMMISSURAL CONNECTIONS. It seems fairly certain that all of the interhemispherical cortico-cortical connections of the region of cortex under consideration pass through the corpus callosum, not through the anterior commissure. The only possible exception involves area 47, on whose interhemispherical connections neither the work reported here nor any other known to the author has thrown any light. These connections have been studied by the Marchi method(Mettler, 1936), by electrical stimulation(Curtis, 1940a&b) and more recently by McCulloch

and his collaborators (Bucy, 1943) with the strychnine method. The following summary is based on these three sources.

(i) *Efferent*. Area 4q shows callosal connections which are only homoiotopic, the connections being extremely well localized to the exactly symmetrical motor focus. Moreover, these connections arise only from the representations of trunk, neck and lower face — *i.e.*, only from motor foci for parts of the soma used almost exclusively bilaterally, not from the foci for movements of the parts used typically otherwise — *i.e.*, feet, hands and upper face.

Table showing homolateral areal interrelations of chimpanzee cerebral cortex as elucidated by the strychnine method (From McCulloch in Bucy, 1943).

AREA STRYCH.	32	24	47	8	6	4s	4r	4q	1	2	5	40	39	19	18	17
32	A	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o
24	+	L	—	—	—	—	—	—	—	—	—	—	—	—	—	—
8	+	—	—	L	—	—	—	—	—	—	—	—	—	—	+	—
6	o	o	?	o	A	+	+	+	+	?	+	o	+	o	o	o
4s	+	—	—	—	—	L	—	—	—	—	—	—	—	—	—	—
4r	o	o	o	o	o	+	R	+	o	o	o	o	+	o	o	o
4q	o	o	o	o	o	o	o	R	+	o	+	o	o	o	o	o
1	o	o	o	o	o	+	+	+	F	?	+	o	+	o	o	o
2	+	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
5	o	o	o	o	o	o	o	+	+	?	F	+	o	o	o	o
40	o	o	o	o	o	o	+	o	+	o	?	F	o	o	o	o
39	o	o	o	o	o	+	o	o	o	o	o	?	o	+	o	o
19	+	—	—	—	—	—	—	—	—	—	—	—	—	R	—	—
18	o	o	o	o	o	o	o	o	o	o	o	o	o	+	A	+
17	o	o	o	o	o	o	o	o	o	o	o	o	o	o	+	L

The + sign indicates well established firing; o, well established lack of firing; L, strictly local firing; R, firing restricted to a large part of the same area; F, firing of whole area; A, same area; —, suppression.

Area 4r. The connection is essentially similar to that from 4q.

Area 4s sends no interhemispherical connections.

Areas 6a and 6b. All parts of both send homoiotopic and heterotopic connections to most of the sensory cortex of the same somatotopic subdivisions. In these must be included areas 39 and 40 — which, while they are part of the arm subdivision, have been fired from face 6 and leg 6a.

Area 8 sends callosal connections to the contralateral area 18, but to no other part of the contralateral hemisphere. This tract arises from its posterior margin anterior to arm 6a.

Area 24 has not yet been proved to have any such connections, but they have not been definitely excluded.

Areas 31 and 32 send hemoiotopic connections but it cannot yet be asserted definitely that no heterotopic connections exist, for the studies do not yet exclude all heterotopic possibilities.

(ii) *Afferent*. The homoiotopic connections mentioned above necessarily indicate that the areas originating also receive homoiotopic connections, but fail to indicate the reception of heterotopic connections from other areas within and without the area under discussion. Hence the receipt of heterotopic connections are capitulated below.

Area 4q receives interhemispheric homotopic connections from area 4q in the same restricted fashion as that in which it sends them. In addition, many parts, if not all, of area 4 receive heterotopic connections from area 6 and from a small portion of the superior parietal lobule lying inside the sulcus postmental superior.

Area 4r. These are essentially similar to area 4q.

Area 4s receives no interhemispherical connection, with the possible exception of one from area 6.

Area 6 receives only homotopic connections.

Area 8 receives no discoverable callosal connections of any kind.

Areas 31 and 32. No heterotopic firing has been found.

ABLATION OF AREA 6A (UPPER PART)

The effects of primary ablation of area 6 will be discussed under four headings: disturbances of movement, forced grasping, spasticity and reflex changes; autonomic phenomena will be discussed in chapter XXIII. Unless otherwise stated the experimental observations are drawn from chimpanzees. This form has been chosen since the reflex disturbances following lesions of area 6 more closely simulate those seen in human beings than do those of other experimental animals.

Attention first came to be centred upon the premotor area through its association clinically with the phenomenon of forced grasping, and the concomitant clinical manifestations which Walshe and others have referred to as "tonic innervation." Owing to the diffuse character of clinical lesions, great uncertainty existed prior to 1932 about whether forced grasping was due in the first instance to a cortical lesion or to subcortical involvement. The demonstration by Richter and Hines (1932) that isolated removal of the premotor area causes forced grasping in the monkey settled the problem of the cortical origin of this phenomenon. The great elaboration of the premotor area in higher primates makes it possible to isolate this region for functional analysis more adequately than in lower vertebrates. The dog and cat have poorly developed premotor areas and, as Woolsey (1933) has pointed out, the results obtained in these forms are clearly not applicable to man. Inferences concerning the functions of human cortical areas must be drawn with the utmost caution even when based on results in monkey and chimpanzee; but the organization of the chimpanzee brain closely approaches that of the human being.

DISTURBANCES OF MOVEMENT. A lesion sharply restricted to area 6a (upper part) in macaque or in chimpanzee is followed by transient weakness of the contralateral limbs. In the macaque this weakness is very slight so long as one does not encroach upon the strip region, manifesting itself chiefly in a reluctance to use the extremity for three or four days following the ablation. The extremity is held in a position of slight flexion at elbow; the knee is extended in the macaque, and flexed in the chimpanzee. By the end of the week its gross motor performance is normal.

However, on close analysis with problem-box technique(ch. xx)in trained animals it has been found that the animal suffers permanent deficit in its capacity to make skilled motor adjustments. The organization of movement patterns, especially those demanding delicacy of movement, is impaired, and only after extensive retraining does the animal relearn how to manipulate simple problems. Deep-rooted habits such as grooming(flea-picking)of hairy surfaces are awkwardly carried out for an indefinite period of time. A gibbon under observation in the Laboratory four years after primary removal of the premotor area still showed awkwardness in grooming movements, and in the capacity to approximate the thumb and index finger-nail in picking up hairs and other small objects. In man the first sign of a disturbance during the course of development of a premotor lesion is a similar disturbance of skilled movement pattern such as those essential for buttoning a shirt, fingering a violin, or playing a piano(Kennard, Viets and Fulton, 1934).

FORCED GRASPING. Involuntary grasping and the associated reactions which appear following lesions restricted to area 6a(upper part)must be discussed in some detail, since the phenomena form a group of basic postural reflexes peculiar to animals having powers of prehension. It is essential first to define terms.

Forced grasping refers to the automatic prehension reaction occurring in primates(including man)after lesions of the premotor area. It consists of slow flexion of the digits in response to gentle contact with certain parts of the palmar or plantar skin; the response itself is generally somewhat variable since it is subject to cortical modification from visual, tactile, proprioceptive and probably from other sensory channels. It is also affected by the position of the body in space. The adjective "forced" is appropriate since it implies both "compulsion" and "automatism" without complete loss of cortical control.

The *grasp reflex*, the basis of forced grasping, is a flexor response of the digits, postural in character, which is integrated subcortically. It is present in monkeys and chimpanzees from which the motor and premotor areas have been removed bilaterally, and its characteristics are essentially unaltered in animals which have been rendered completely thalamic through removal of both hemispheres. In bilateral motor-premotor preparations the grasp reflex does not fluctuate as a result of cortical integrations, but it is affected by change of position of the body in space along with other postural reactions(Fulton, 1934).

Groping refers to the sequence of rhythmic reaching movements of an extremity preparatory to the grasp. Unlike the grasp reflex, groping is a cortical reaction arising chiefly from visual stimuli, and it is seen in most marked form in monkeys from which the frontal and premotor areas have been removed bilaterally. It disappears when the pyramidal tract is destroyed and in premotor-frontal animals it ceases entirely when vision is abolished. Groping from unilateral frontopremotor lesions has been noted in monkeys, but it is subject to unpre-

dictable fluctuations. It is clear from these observations that groping is an "automatic" movement integrated at the cortical level.

The phenomenon of groping is closely linked with *perseveration*, for an animal which gropes generally tends to hold postures beyond their period of usefulness, and to continue in the performance of rhythmic movements long after their purpose has been achieved. Thus, if a bilateral frontopremotor macaque is given a piece of sugar, the animal continues to crunch rhythmically after the sugar is completely dissolved. The phenomena of groping and the perseveration of groping movements are clearly cortical, since they disappear when the pyramidal tracts are removed. Groping, which depends upon visual stimuli, should be carefully distinguished from the somewhat similar *rhythmic righting movements* seen in cortically paralyzed primates and in thalamic preparations when the position of the body is changed in space (Bieber and Fulton, 1938). These rhythmic righting movements come from the labyrinth and the body proprioceptors rather than from the visual pathways.

The phenomenon of forced grasping comes on within a few minutes of ablation of the premotor area, both in monkeys and chimpanzees, and it is evidently due to withdrawal of extrapyramidal inhibition acting upon subcortical centres. In monkeys the phenomenon wanes after four to six days, and generally disappears within a week after the premotor ablation. In chimpanzees it may persist for ten days to two weeks. It returns on both sides (and in all four extremities) when the second premotor area is removed; but it dwindles again, as does spasticity, within a few weeks to a month after the second ablation. During the terminal period the grasp is subject to gross fluctuations: frightening causes intensification; distraction by food is likely to cause relaxation, and the phenomenon is subject to fluctuations from other sensory stimuli integrated at the cortical level. The grasp reflex becomes permanent and predictable only when areas 4 and 6 have been removed from both cerebral hemispheres. In these circumstances its relation to other postural reflexes can be clearly brought out.

Grasp reflex and corpus callosum. Armitage and Meagher (1933), Richter and Hines (1932) and Kennard and Watts (1934) have all found that section of the corpus callosum does not in itself produce forced grasping, and the last writers observed that in a unilateral or bilateral premotor preparation from which forced grasping had disappeared, section of the corpus callosum did not cause the symptom to return. The corpus callosum, therefore, does not play an important part in causing the grasp. See also Penfield and Erickson (1941).

Centre for grasp reflex (ch. x). The grasp reflex which underlies forced grasping becomes permanent in the bilateral motor-premotor preparations as described in a preceding chapter. It therefore can be studied in most preparations and analyzed without modification from cortical levels of integration. The grasp ap-

pears to be dependent upon the integrity of the tegmentum, the presence of the striatum and anterior part of the thalamus being unessential to the response. Further studies, however, are needed to determine the precise locus of the reflex in terms of anatomical nuclei.

GRASP REFLEX AND POSTURAL REFLEXES. When areas 4 and 6 have been removed from both sides of an adult macaque, the animal suffers complete volitional paralysis, lying on its side and assuming the reflex posture of a thalamic monkey (ch. x; Magnus, 1918, 1922). Thus when in the lateral position there is pronounced extension of the underlying limbs, with flexion of the limbs on the upside (fig. 49); when turned over, the pattern of response is reversed. *It is highly significant that the grasp reflex when the animal is in the lateral position is well marked only in the extremities on the upside: thus, if the animal is lying on its right side, the left hand and left foot exhibit a vigorous reflex* (ch. x). From the fact that the grasp follows other body righting reflexes acting upon the body, Bieber and Fulton (1938) concluded that the grasp has become, in higher animals, a part of the righting reflex mechanisms. In the presence of the cortex the grasp subserves other more highly integrated functions, but in the absence of the cortex it reverts to the primitive group of postural reactions from which it apparently took origin.

Forced grasping following a *unilateral* area 6 lesion is similarly responsive to change of position in space. It is generally impossible to obtain forced grasping when the affected side is down, but it comes on when the affected extremity is on the upside. Thus, it follows that in clinical cases with unilateral lesions forced grasping is most likely to be observed with the patient in the lateral position and the suspected extremity on the upside. Changes in intensity of forced grasping with change in position have been described in clinical cases (Viets, 1934).

Sensory components of grasp reflex. Forced grasping and the grasp reflex may both be obtained in sensitive preparations by applying gentle pressure to the skin of the plantar and palmar surfaces. In man and monkey stroking the skin over the metacarpo-phalangeal joints is often an adequate stimulus; the cutaneous sense organs are, however, unessential to the grasp reflex in the monkey, since the response persists when the entire palmar or plantar skin is novocainized (Bieber and Fulton, 1933). Gentlest contact with the tips of the fingers will then serve to bring on the grasp, due apparently to the stretch of the digital tendons. When the tendons have been denervated through appropriate posterior root section, *e.g.*, from the third to the eighth cervical level, the grasp reflex is abolished, while the animal is at rest, but it can be evoked by any manoeuvre which causes the shoulder muscles innervated by the upper thoracic segment to be placed under stretch. When the muscles of an entire upper extremity of a bilateral area 4-and-6 ma-

caque are deafferented through posterior root section from third cervical to eighth thoracic levels, the grasp reflex as such is destroyed, but the pattern of grasping may be made to appear and be of sufficient intensity in the deafferented extremities to support the animal's weight, *if the body as a whole is moved through space*. Presumably the labyrinth can influence the completely deafferented extremity. The grasp reflex may be regarded as a fundamental pattern of response in the neurological makeup of primates.

Grasp reflex in infants. The grasp reflex in human infants exhibits characteristics entirely similar to those described in the thalamic monkey, *i.e.*, it is most pronounced in the uppermost hand when the child lies in the lateral position, and grasping is similarly augmented by moving the child's body rapidly through space. It also has cutaneous and proprioceptive reflexogenous zones. For full details concerning grasping in infant monkeys see Richter(1931) and the comprehensive monograph of Halverson(1936-37) on human infants.

Further evidence that the grasp reflex is a part of the postural mechanism comes from data on labyrinthectomized monkeys(Fulton and Dow, 1938). When areas 4 and 6 are removed from both sides of a bilaterally labyrinthectomized macaque, the monkey assumes the thalamic reflex posture just described, and is responsive to neck reflexes. In these circumstances the grasp reflex is modified in a striking manner by rotation of the head. Thus with the animal in a supine posture the grasp is completely inhibited on the side towards which the chin is rotated, and augmented on the opposite side. This is entirely in harmony with the fact that rotation of the chin causes extension of the extremities as a whole on the chin side and flexion contralaterally.

SPASTICITY. The states of spasticity which follow various lesions of the frontal lobes have been much under discussion and it is essential at the outset to indicate what is meant by the term. A muscle is said to be spastic if on passive movement a certain *quality* of resistance is encountered, intense at first and then rapidly diminishing as the range of movement increases("clasp-knife" phenomenon, or "lengthening reaction," ch. ix). Associated with this characteristic form of resistance are exaggerated deep reflexes, "shortening reactions," etc., which closely simulate the rigid states seen in cats following decerebration. Spasticity, indeed, resembles decerebrate rigidity not only in the quality of the resistance, but in its *distribution*. Thus the muscles most prone to exhibit spasticity are those which normally counteract the force of gravity, *e.g.*, the extensors of the hind limbs. These similarities between clinical spasticity and decerebrate rigidity have led Denny-Brown to define spasticity as a state of abnormal exaggeration of the stretch reflexes — exag-

generation of stretch reflexes being also the basis of decerebrate rigidity (ch. ix).

Primary removal of area 6a(upper part)without encroaching upon the strip region causes abnormal resistance, transient in character, affecting all muscles, proximal as well as distal, of the extremities opposite to the lesion; but the quality of the resistance and also the distribution does not conform with that characteristic of the spastic state, *i.e.*, it is a soft cataleptoid resistance equal in quantity through all ranges of passive movement. The belief that lesions of area 6 are concerned with spasticity was based largely upon another type of experiment. If, instead of removing area 6 as a primary operation, it is ablated *after* area 4 has been removed, a previously flaccid extremity(or one spastic at distal joints, ch. xx), becomes highly spastic and remains so(fig. 101). The explanation of this apparent discrepancy lies in the fact that the intensity and duration of spastic resistance are functions, not of any one area, but of *the extent of interruption of the extrapyramidal cortical projections*. The distribution of spasticity depends to some extent upon the region ablated(Hines, 1937). The evidence for this conclusion has been slowly acquired and is based upon various ablation experiments, which may be summarized as follows:

Cerebral hemisphere. When an entire cerebral hemisphere is removed from a monkey or chimpanzee the animal suffers at first a flaccid paralysis which, after 4 to 5 days, gradually passes over into a state of conspicuous spasticity. A chimpanzee which survived in good health for 3 months after removal of the left hemisphere exhibited extreme spasticity affecting all muscles of the right side, proximal as well as distal. The same is true of man(Karnosh and Gardner, 1941).

Areas 4 and 6. Another chimpanzee, from which areas 4 and 6 were removed from the left hemisphere, developed an enduring spasticity affecting proximal and distal joints alike, also flexors and extensors; at first the spasticity was as intense in degree as that of the previous chimpanzee, but over the period of 6 months' survival, the spasticity became slightly less in degree than that of the hemidecorticated chimpanzee.

Areas 9-10-11-12. Removal of the frontal association areas at a primary operation has not caused a trace of spasticity; but in a chimpanzee in which the frontal association areas were removed a year *after* areas 4 and 6, there was slight augmentation in the spastic state.

Area 4. As indicated in the last chapter, lesions restricted to area 4, exclusive of the strip region, both in monkey and chimpanzee, give rise to a primary paralysis, flaccid at first in all joints, but later passing through a stage of transient spasticity of digits, ankle and wrist. Spasticity has not been seen in proximal joints following such area 4 lesions.

Strip region. When the transitional cortex between areas 4 and 6(which contains a sparse population of large pyramidal cells in the fifth layer)is removed from

the macaque, Hines(1937) has observed a state of spasticity affecting the proximal joints. When area 4 plus the strip region is removed from the macaque, moderate spasticity develops at all joints; when in addition area 6 is removed, the spasticity becomes conspicuous and permanent.

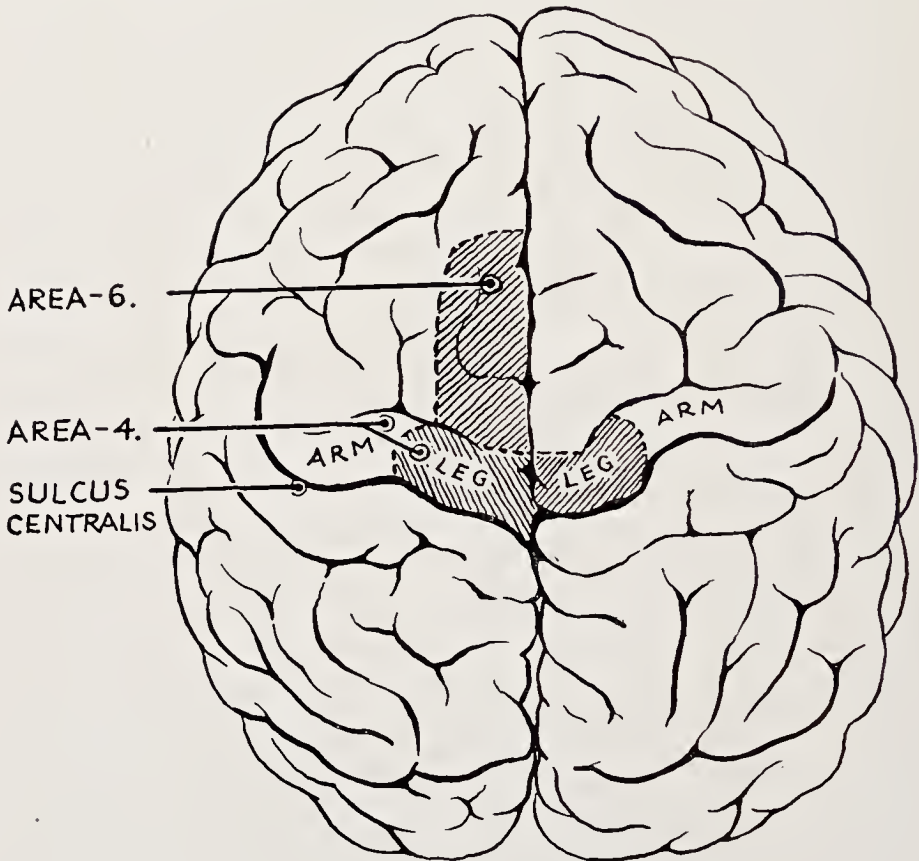


FIG. 101. Diagram of cerebral hemisphere of chimpanzee showing ablations of area 4a(leg), removed respectively Jan. 21, 1932(left), and March 4, 1932(right). Following each procedure animal suffered flaccid paresis from which it gradually recovered *without developing spasticity*, except possibly in digits. Dec. 6, 1932, part of area 6 indicated in diagram was ablated and immediately thereafter animal became spastic on right side and remained spastic in right leg until death July, 1935(Kennard and Fulton, *Brain*, 1933, 56, p. 216).

Section of pyramids alone. To Tower and Hines(1935) we owe the observation that primary section of the pyramids in the monkey causes no one of the spastic phenomena mentioned above; indeed, pyramid section in monkeys causes a *flaccid* paresis, and the extremities continue to be flaccid throughout the period of postoperative recovery(ch. xx).

Areas 3-1-2. In unpublished studies Walker finds that primary ablation of the postcentral gyrus in the chimpanzee causes no spasticity. If, however, it is associated with a lesion entirely confined to area 4 a spasticity most marked in the distal muscle groups is present.

From these observations the conclusion is drawn that in monkeys and chimpanzees the phenomenon of spasticity is an *extrapyramidal* release of cortical origin. The extent and distribution of the release varies with the species of animal and with the type and extent of the extrapyramidal destruction in the cortex. Thus removal of extrapyramidal projections from area 4 causes a delayed and transient spasticity of the digits. Removal of extrapyramidal projections from the strip area causes the spastic release to extend into more proximal joints. If in addition the extrapyramidal projections of 6 are destroyed, there is an *enduring* state of spastic hemiplegia affecting all joints, and involving to some extent both extensor and flexor muscle groups. The ultimate distribution of spastic resistance generally confers a definite posture upon the affected extremities which varies with the position of the body in space.

REFLEX CHANGES. In considering the reflex changes associated with premotor lesions it is essential to distinguish those which follow isolated removal of the premotor area, from those which develop when area 6 is removed secondarily to a lesion of area 4.

Primary ablation. A lesion sharply restricted to area 6a causes moderate increase in tendon reflexes throughout both extremities on the opposite side, including the digits. The changes are more marked in chimpanzee than in monkey; the toes tend to be more affected than the fingers, *i.e.*, Rossolimo's tendon reflexes of the toes can be more often elicited than Hoffmann's reflex of the fingers (see below). The toes also tend to spread (fanning) when the plantar surface is stroked, but Babinski's sign of the up-going hallux is absent. All these changes are transient, disappearing within a week or ten days.

Secondary ablation. When area 6a is removed some months after a lesion of area 4ab, the reflex changes are conspicuous and enduring and are essentially those which accompany the spastic state in man. They may be summarized as follows:

In the first place, the deep reflexes exhibit marked augmentation; there are also certain specific neurological signs of clinical significance.

Signs of Rossolimo and Mendel-Bechterew. Flicking of the toes (Rossolimo) or tapping the dorsum of foot (Mendel-Bechterew) over the metatarsophalangeal joint tends to initiate involuntary flexion of all the toes including the hallux. With extrapyramidal lesions of the cortex these reactions are greatly exaggerated. Rossolimo's manoeuvre is perhaps the most sensitive mode of eliciting these tendon reflexes, and in chimpanzees this response has persisted following a secondary premotor lesion for several years after spasticity and the other more obvious premotor symptoms had greatly diminished. It is interesting to recall that Rossolimo in his

original monograph(1895)stated his belief that exaggeration of this reflex was not due to interruption of the pyramidal tracts, but rather to impairment of an hypothetical tract under cortical influence which descended along with the pyramidal fibre(Schick, 1933).

Sign of Hoffmann. Corresponding to Rossolimo's sign in the foot is a tendon phenomenon of the fingers, known under the eponym of Hoffmann(see Echols, 1936, and Bendheim, 1937). Flicking the finger-nail of one digit in premotor preparations causes a marked involuntary flexion of all the other digits. In one chimpanzee following bilateral motor and premotor lesions of the hand area, the Hoffmann sign persisted unchanged over a period of two years. After an isolated premotor lesion it generally disappears within a few weeks.

Fanning sign of Babinski(1903). Simple extension of the toes is seen following a lesion restricted to area 4. This is the classical Babinski response(1896, 1898). When the premotor area is also destroyed, the toes extend following plantar stimulation and then show marked lateral deviation or fanning. The fanning sign may therefore be taken to indicate involvement of the premotor projection system.

A comparison between the pathological reflexes in motor and premotor lesions respectively is given in the following table.

Table showing reflex changes following unilateral upper motor neuron lesions(cortical)

	Motor (Pyramidal)	Premotor (Extra- pyramidal)	Combined Motor and Premotor
Babinski	+	o	++
Chaddock	+	o	+
Gonda	+	?	+
Spasticity	o	++	+++
Toe fanning	o	+	+
Rossolimo	o	+	++
Mendel-Bechterew	o	+	++
Forced grasping	o	+	+
Hoffmann	o	+	++
Tendon	+ *	++	+++
Abdominal	o	?	o
Vasomotor disturbance	o	++	++

* Depressed or absent in early stages following a motor area lesion.

The reflex changes just described are of localizing significance in Clinical Neurology and yield information concerning the size and position of an unexplored lesion of the frontal lobe. From the work of Marion Hines it is likely that when forced grasping is present the lesion involves the anterior part of the premotor region(area 6a β); isolated spastic phenomena bespeak lesions of the middle part of area frontalis agranularis; pareses of isolated movements and flaccidity bear evidence of lesions of the posterior part of area frontalis agranularis. Ablation of the other parts of area 6, *i.e.*, areas 6b, and 6a β , have been studied by Green and Walker(1938).

Ablation of eye fields. The frontal eye fields have been ablated in

macaques by Levinsohn(1909), Hirasawa and Kato(1935), Levin(1936), Kennard and Ectors(1938), Kennard, Spencer and Fountain(1941); and in a chimpanzee by Bender and Fulton(1938). Such a lesion has rather striking effects, not only on the eyes, but upon movements and behaviour. As with premotor lesions, bilateral ablation is considerably more disturbing than unilateral.

Unilateral ablation(area 8). Following removal of the frontal eye field in the macaque(without including the adversive field which lies more medially), the animal's head turns up to the side of the lesion and there is a conspicuous, but transient paralysis of conjugate deviation of the eyes to the opposite side; there is no inequality of the pupils and no difficulty in reflex opening and closing of the lids. In addition, the animal *circles involuntarily toward the side of the lesion*. Kennard and Ectors have referred to this phenomenon as "forced circling." The period of circling coincides with that in which the animal exhibits paresis of lateral deviation of the eyes, but it may continue long after the paresis has disappeared. Extirpation of no other cytoarchitectural area (*i.e.*, 9-10-11-12, 6, 4, 3-1-2, 18, 17, 5 or 7) of the cortex causes circling.

In addition to the effects on the ocular muscles and gait, the animals fail for several days to recognize the nature of objects brought into the visual field opposite to the lesion, although they clearly perceive light on this side. The transient visual disturbance is believed to be due to disorganization between retina and extraocular proprioceptors(see Sherrington, 1918; Graham Brown, 1922).

Bilateral ablation. When both eye fields are simultaneously removed a curious syndrome results of transient object-vision blindness, and an expressionless facies akin to the clinical syndrome of "Parkinsonism" (Kennard, 1939; see W. K. Smith in Bucy, 1943).

Occipital eye fields. The effect on vision of ablation of the occipital lobes has been described in detail in chapter xvii. The motor effects are transient: according to the recent work of Barris(1936), the pupils react normally to light after unilateral ablation of the pupillary constrictor centre(posterolateral gyrus—area 19), but for several weeks after the lesion the animals show conspicuous "hippus," *i.e.*, alternate constriction and dilatation of the pupils unaccompanied by changes in accommodation(Marchi degenerations were traced to the pretectal nucleus and superior colliculus). There is also pupillary inequality, the pupil on the opposite side being wider(Waller and Barris, 1937).

Ablation of areas 17 and 18 may cause transient paresis of conjugate deviation of the eyes to the opposite side, but this is much less pronounced than the paresis which follows ablation of area 8. In a chimpanzee observed by Spence and Fulton(1936) the pupils were equal immediately after complete ablation of areas 17 and 18, and the eyes were capable of full conjugate deviation in both directions, but tended at first to deviate to the side of the lesion.

Primary ablation of the temporal lobes, partial or complete, is unaccompanied by motor deficit, even when bilateral(Jacobsen, 1936). For the motor effects of parietal lobe ablation see chapter XIX.

VOLITIONAL MOVEMENTS AND EXTRAPYRAMIDAL PATHWAYS

Isolated volitional movements thus depend upon the integrity of area 4 and the pyramidal tract; it has indeed long been a working hypothesis of Clinical Neurology that *all* volitional movements, be they isolated in character or deep-rooted synergies, are mediated by the pyramidal pathways. Analysis of the effects of ablating area 4 indicate, however, that this hypothesis is too sweeping, for chimpanzees and the lower monkeys, after complete destruction of the Betz cells, recover sufficient power to carry out progression movements, to climb and to feed themselves. Foerster(1936b) has shown in man that purposeful movements of extrapyramidal origin are gross in character and that finer movements, *e.g.*, of the digits, are never seen. In studying the late phases of recovery from a bilateral lesion of area 4 in animals it is often difficult to distinguish an isolated movement from the gross deep-rooted synergies which Foerster and others have described in man, but, as in man, fine finger movements are never regained(Hines, 1937).

When areas 4 and 6a are bilaterally removed from an adult monkey, the animal is reduced virtually to the thalamic reflex status, exhibiting all of the thalamic patterns of response of Magnus(ch. x); it is unable to feed itself, to run or climb, and cannot even after 4 months maintain itself in the horizontal posture. If in one hemisphere as little as 15 to 20 per cent of "agranular" frontal cortex remains intact, the animal ultimately regains some degree of volitional movement in all four extremities(Fulton, 1936).

INFANT MONKEYS. The situation is somewhat different when a cortical ablation is carried out in infancy. Kennard(1938) has studied a macaque from whom areas 4 and 6a were removed shortly after birth(see also Kennard and McCulloch, 1943).

When such procedures are carried out during the first weeks of life, little motor deficit is immediately detectable. Several of such animals have been raised to maturity over a period of two to three years, and their motor coördination closely studied. The oldest animal (observed at five years of age) progressed like a jack-rabbit, rhythmic progression synergies being poorly developed. It was able to climb and feed with its hands and carried out other fairly well executed movements of moderate complexity. When the cerebral hemisphere of one of these animals was exposed five years after the original lesion, the depths and margins of the scar were inexcitable; on faradic stimulation, however, flexor synergies *could be obtained from the postcentral convolution*. The frontal association areas of this animal were inexcitable, but their ablation caused unmistakable increase in motor paresis of the opposite extremity. When, therefore, the motor and premotor areas are removed soon after birth, it is clear that the extrapyramidal projections in the postcentral and frontal association areas are capable of assuming some degree of the motor control over lower centres, and thus play a part in restitution of motor function.

In the detailed monograph of Hines and Boynton (1940) on maturation of excitability in the precentral gyrus of monkeys and in Hines' (1940) later correlated study of the development and regression of postures in the young macaque, full details are given concerning the excitability of the cortex in macaque foetus as young as 66 days gestation and the analysis is continued in infants through the first year of life. From 66 to 125 days gestation gross movement patterns were obtained which were designated "holokinetic," being associated with definite patterns of progression movements seen at this time of development. Idiokinetic movements, such as activation of a single digit or joint, tended to appear during the first four months of life with gradual disappearance of holokinetic movements from the precentral gyrus itself. This process of maturation continued until the adult type of topographical projection emerged with point-to-point stimulation of the precentral gyrus. Hines also describes areas causing inhibition of resting posture which she designates "chaliasis" — hence chalastic foci. These likewise were demonstrable in the foetal cortex. In her analysis (1942) of the development of reflexes and postures Hines associates patterns of movement with her previous analysis of the maturation of the electrical excitability of the cortex. The work harmonizes closely with Kennard's studies of the effects of ablation at different ages.

Ipsilateral control. The importance of bilateral motor representation in the hemispheres has become obvious both from ablation studies and from observations on direct stimulation (ch. xx). If a small portion of the "agranular" frontal cortex of one hemisphere remains intact, volitional movements are still possible in all four extremities (even though the opposite hemisphere may be completely removed). What part do these ipsilateral projections in the cortex play in functional restitution from unilateral lesions? That their participation is direct, even in man, is becoming daily more evident. Thus Karnosh and Gardner (1942) have described cases of human beings who were able to walk with a stick several years after ablation of one cerebral hemisphere. Monkeys similarly move about with surprisingly good coördination after a hemisphere

is removed; a chimpanzee, following unilateral hemispherectomy, was able to carry out primitive synergies, evidently volitional, 6 to 7 weeks after the ablation (Walker and Fulton, 1938). When the animal was sacrificed some two months after operation, dramatic inhibition of the spasticity of the hemiplegic extremities could be evoked by weak faradic stimulation of the remaining (ipsilateral) premotor area. Thus while ankle clonus was in progress, a weak stimulus to area 6a produced an immediate inhibition of the clonus, and an almost equally prompt relaxation of the extensor tonus of the gastrocnemius muscle. Pointing in the same direction is the observation that removal of the second leg area from a chimpanzee always gave more profound paralysis and more enduring reflex changes in the opposite extremity than that following removal of the first foot area (Fulton and Keller, 1932).

The factors involved in restitution of motor function in the cerebral cortex thus include not only the age of the subject and activity of the other extrapyramidal motor projections in the same hemisphere, but the influence of the ipsilateral projection (pyramidal and extrapyramidal).

SUMMARY

The extrapyramidal motor projections are primarily concerned with postural adjustments of the skeletal musculature, but they are also capable of mediating certain deep-rooted volitional synergies. From certain extrapyramidal regions, moreover, specific regulatory functions have been established, such as pupillary constriction (area 19), external ocular movements (area 8), vocalization (6a β), respiration (area 13), and autonomic functions which will be discussed in chapter XXIII. The evidence for these conclusions rests upon the following observations.

STIMULATION — Area 6a (Premotor area). Stimulation of the premotor area under light ether anesthesia may evoke specific movements similar to those from the motor area; these movements are dependent upon the integrity of the motor area, since they disappear when this is destroyed or when the cortex is superficially incised between areas 4 and 6. Stereotyped movements, often accompanied by turning of the head (adversion) and torsion of the body, are also obtained from area 6a; these persist after the removal of the motor area and degeneration of its projection fibres, disappearing only when the premotor area is undercut.

Area 6a α (lower part) and area 6b α yield substantial movements of the mouth, salivation, chewing, coning of the lips, etc.

Area 6bβ on stimulation causes inhibition of respiratory movements, probably through spread to area 13.

Area 8, the eye field, causes specific movements of the eyes, generally conjugate deviations (with turning of the head to the opposite side).

Area 19 gives strong pupillary constriction and occasionally conjugate deviation. Areas 17 and 18 are without motor effect.

Areas 3-1-2 facilitate movements from area 4 and in man are said to give isolated movements which are dependent on the integrity of area 4.

Area 5 gives adversive movements similar to those obtained from area 6aβ.

Stimulation of one area also causes specific effects on other cortical areas. These are summarized in figure 100.

ABLATION. The symptoms which follow removal of area 6a vary in accordance with whether the ablation is primary, or secondary to removal of area 4. Primary ablation causes disturbances in skilled movements (demonstrated by training techniques), and also characteristic postural disturbance, consisting of a soft cataleptic rigidity which is approximately equal in all muscle groups and equal in quantity from the beginning to the end of passive movement. Deep reflexes are moderately increased, but all changes, except the disturbance of skilled movements, are transient. When area 6 is removed *after* ablation of area 4, great increase is observed in movement disability; any existing spasticity is greatly augmented; deep reflexes become uniformly exaggerated, and specific neurological signs such as those of Rossolimo (toes), Hoffmann (fingers), and the fanning sign of Babinski all appear and, in the chimpanzee, remain permanently.

Forced grasping appears following a primary premotor ablation and evidence is presented that forced grasping is a particular manifestation of the thalamic grasp reflex, and hence a postural reaction peculiar to the prehensile fingered primate. The grasp reflex is influenced by the neck reflexes as well as the body righting reflexes. The phenomenon persists after anesthetization of the skin, and destroyed by complete deafferentation of the upper extremity.

Ablation of area 8 leads to transient visual hemiagnosia, paresis of conjugate lateral deviation of eyes and to circling of the animal toward the side of the lesion. Bilateral ablation of area 8 causes great increase in spontaneous motor activity. The motor effects of ablation of areas 19, 3-1-2, 5, 7, 22, etc., are briefly described.

XXII

CEREBRAL CORTEX: THE FRONTAL ASSOCIATION AREAS *

HISTORICAL NOTE

The frontal areas have been investigated by neurologists of every country. The earliest experiments were those of the French neurologist Flourens(1824), who, on the basis of ablation studies, cast to the four winds the phrenological doctrines of Goll and Spurzheim. Flourens denied the existence of functional localization, except in the most general sense, and he attributed to the frontal lobes, acting in harmony with the rest of the brain, the higher perceptual, associative and executive functions of the mind; and he also rendered an important service in the history of Neurology by overthrowing the naïve concepts of phrenology. During the last part of the nineteenth century the frontal areas became once more the subject of experimental study at the hands of David Ferrier in England, Luciani and Bianchi in Italy, Pavlov in Russia, Goltz, Jacques Loeb and Flechsig in Germany, and Franz and Lashley in America; more recently the frontal areas have been studied by clinical observers, particularly among the neurosurgeons(see Geoffrey Jefferson, 1937). It is unnecessary here to give more detail concerning historical developments, since these have been fully described by Bianchi(1922), Franz(1907), Brickner (1936), Rylander(1939)and Freeman and Watts(1942).

In approaching the functions of the frontal association areas one is brought face to face with activities which are difficult to describe in physiological terms. The types of deficit observed do not relate to simple reflex disturbances or even to failure of skilled movements; they have rather to do with alterations in "behaviour." For want of a better term they have been designated "intellectual deficits," and the purpose of this chapter is to define in an objective manner the character of these "deficits" both in animals and in human beings from which the frontal areas have been removed.

The frontal association areas comprise all cortical tissue lying rostral to areas 6 and 8, and on account of their great size in man this part of the cerebrum is sometimes inaccurately referred to as "the frontal lobe." The "frontal areas" are made up of several architecturally discrete parts, all of which are distinguishable histologically from the motor and

* I am indebted to Dr. Carlyle Jacobsen for assistance in the revision of this chapter.
J. F. F.

premotor areas by the presence of conspicuous small-celled "granular" layers, and by the virtual absence of motor cells from layer v(ch. xv). In man and monkey areas 9, 10, 11 and 12 lie toward the frontal pole, more rostrally areas 45 and 46(lateral surface), areas 24 and 25 (medial surface) and areas 13 and 14(orbital surface) as indicated in figure 102. In man the anterior pole of the frontal lobe is often spoken of as the "prefrontal area" — a term sometimes also used synonymously with "frontal association areas."

GENERAL FUNCTIONS

The state of knowledge of the frontal association areas prior to 1930 might be summarized as follows: all observers agreed that areas 9 and 10 in man and monkey are wholly *inexcitable* to ordinary monopolar faradic stimulation. In some maps of the cortex the eye fields(area 8) encroach upon areas 9 and 10, but this apparent overlapping is probably due to spread of stimulating current(W. K. Smith, 1935, 1936). There is one other discrepancy, that the frontal pole of the cat(in area 9 and partly in 6) contains a focus which causes dilatation of the pupil, but in the monkey and chimpanzee no corresponding region has been found in areas 9 and 10, such pupillary effects invariably being evoked from area 8. With regard to *reflex* changes following ablation of the frontal area, there was greater difference of opinion. In cats and dogs changes in posture were said to occur when the frontal area was removed, even when the premotor region was not encroached upon(see Langworthy, 1928). *No reflex changes in the skeletal muscles, and no obvious alterations of posture follow extirpations sharply restricted to the frontal areas of monkeys or chimpanzees.* The early primate literature was somewhat confused on account of the fact that the rostral part of the premotor area was often encroached upon in making ablations, and motor weakness was encountered in some of the early experiments, *e.g.*, those of Ferrier, Schäfer and Bianchi(1922). Recent experience has indicated that in monkeys and chimpanzees there is no conspicuous disturbance of reflexes of the extremities or change in motor power after *primary* extirpation of the frontal areas. Similarly, no sensory changes have been observed except for increased hunger.

Bianchi(1922) and others have described a characteristic abnormality of *behaviour* following bilateral removal of frontal association areas of monkeys; when only one frontal area is removed, no disturbance of any

sort, even in the sphere of behaviour and higher intellectual functions, can be detected. When both frontal areas are removed, the animal tends to become restless, pacing the floor constantly and generally losing weight in spite of ravenous appetite and the consumption of abnormally large quantities of food. There is great distractibility and a marked tendency to shift from one activity to another.*

In human beings various peculiarities of behaviour have been observed which have simulated changes seen in animals, *i.e.*, in addition to distractibility, restlessness, there is a tendency towards boastfulness and general euphoria with surprising lapses of judgment and decision (Brickner, 1936). The most thoroughly studied human cases in the literature are those of German and Fox(1934) and Penfield and Evans (1935), in which unilateral extirpations were carried out, and those of Brickner(1936), Rylander(1939) and Freeman and Watts(1942), in which there had been a bilateral removal of the frontal areas. Some clinicians suggest that the fundamental difficulty lies in a failure of synthesis.

BEHAVIOURAL STUDIES ON MONKEYS AND CHIMPANZEES

The syndrome of the frontal areas both in man and animals can be broken down into changes in spontaneous behaviour(restlessness, hypermotility) and "intellectual" deficits.

HYPERMOTILITY (AREA 13). The controversy concerning the pronounced motor hyperactivity which generally follows extensive bilateral ablations of the frontal association areas has been clarified through the disclosure of Ruch and Shenkin(1943) that maximal hyperactivity develops in monkeys following isolated bilateral ablation of area 13 (orbital surface of the frontal lobes, see fig. 102). The restlessness noted by Bianchi(1922), Jacobsen(1931) and others following frontal area lesions (that may or may not have included area 13) was usually conspicuous, but occasionally, and for no obvious reason, it failed to develop. Kennard, Spencer and Fountain(1941) observed that the larger their lesions the greater the hyperactivity, and there was a suggestion that encroachment on area 8 increased the symptom; similarly Richter and Hines (1937) observed that when the lesion passed sufficiently caudal to nip the

* Klüver(1933) observed that when a bilateral frontal monkey is offered a grape it quickly takes it and carries it toward its mouth. If a second grape is offered before the first reaches the mouth it drops the first grape and takes the second, and so on until the floor about the animal is covered with grapes and the monkey has not eaten a single one.

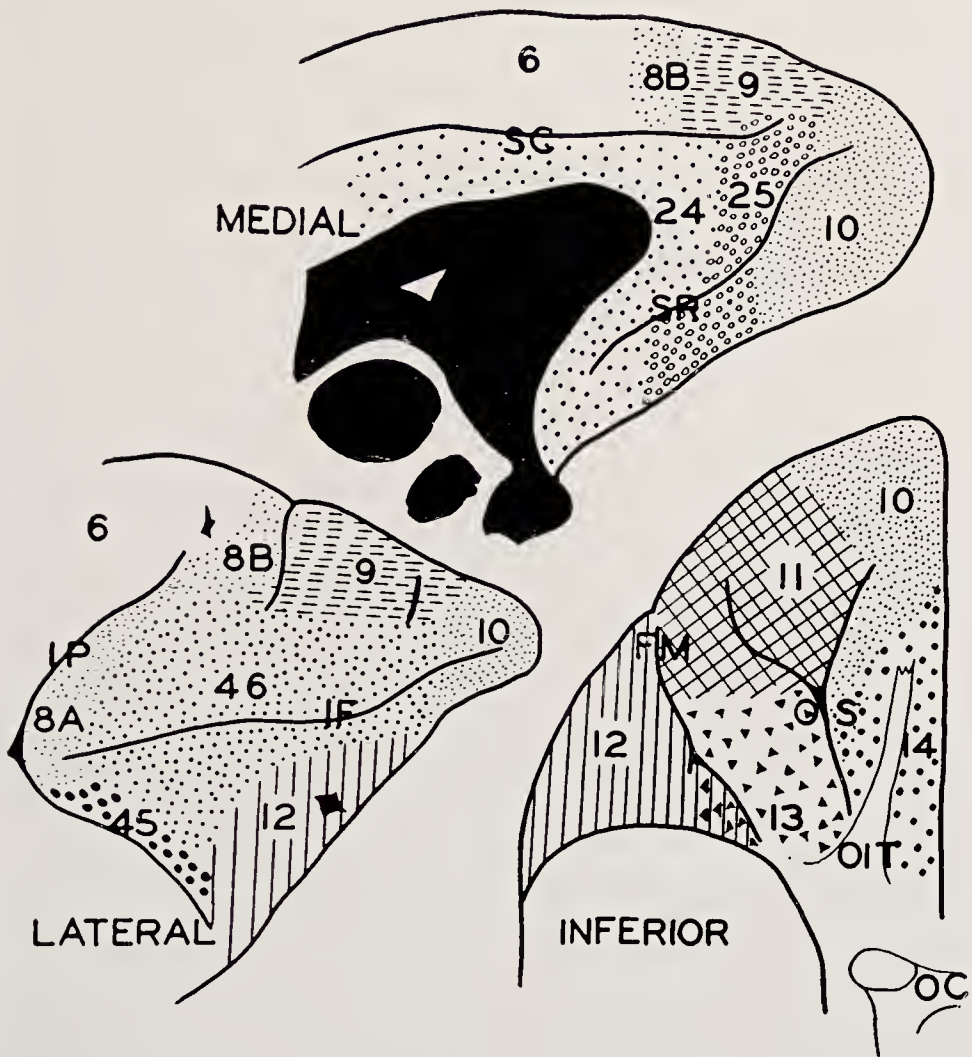


FIG. 102. A map of the cytoarchitectural areas of the prefrontal cortex. Area 13 lies medial to the frontomarginal sulcus, but when the latter does not reach posteriorly to the parolfactory region area 13 extends laterally as indicated (From Walker, 1940).

tip of the caudate nucleus, there was augmentation of activity. It happens that these more posteriorly situated lesions would also tend to encroach upon area 13; and since isolated removal of this area gives of itself maximal activity, it is probable that ablation of area 13, or interruption of its projection fibres, is primarily responsible for the state of extreme hyperactivity which may develop following bilateral frontal lesions.

In this connection it is no doubt significant that Bailey and Sweet (1940) have found that stimulation of area 13 causes sharp inhibition of gastric peristalsis as

well as of respiration; it does not follow, however, that the hyperphagia so often associated with frontal lesions is due to interruption of area 13 projections; for Ruch and Shenkin were unable to detect hyperphagia in their bilateral area 13 preparations. It is probably significant that the sham rage and hyperactivity observed in the cats of Fulton and Ingraham(1929) with prechiasmal lesions developed after injuries closely similar to those of Ruch and Shenkin.

Fresh light upon the frontal areas has been recently obtained through the behavioural studies of Jacobsen(1935, 1936, etc.), Finan(1939) and Malmo(1942) upon trained monkeys and chimpanzees. The following account is based largely upon their work.

“INTELLECTUAL DEFICIT” IN MOTOR AND PREMOTOR ANIMALS. — *Motor area.* In a trained animal injuries of the motor area result merely in difficulty and awkwardness in executing previously learned manoeuvres, but the pattern of the movement as such is not impaired; indeed, as Rothmann(1907) and Lashley(1924) first pointed out, the animal can execute the same pattern of movement with one of the unimpaired extremities (ch. xx). There is thus no suggestion of a loss of memory as a result of destroying the motor area, even when the lesions are bilateral.

Premotor area. With premotor injuries the paresis is less severe and the nicety of individual movements but slightly disturbed. However, when confronted with problem-boxes the animals showed great difficulty in executing the patterns of movement necessary, for example, to undo a hook, or to pull a rope latch. The animal could pick up the rope, but did not execute the next obvious step in the manoeuvre, namely, of pulling it. Lesions of the premotor region thus did not cause gross motor deficit, but execution was made difficult because the *organization* of these movements into patterns of response, even when of a very simple character, was greatly disturbed; a long period of retraining was often necessary before the manoeuvres could be relearned. It is significant, however, that the patterns could be relearned.

DEFICIT AFTER BILATERAL REMOVAL OF FRONTAL AREAS. In analyzing the behavioural changes after removal of the frontal areas, Jacobsen, Finan and Malmo have employed several types of experiments: (i) the problem-box; (ii) the stick-and-platform problem; (iii) delayed reaction test and twelve temporal discrimination tests.

Problem-box. Observations made with problem-boxes indicate that after lesions of the premotor areas the animal experiences difficulty in executing complex motor patterns. The defect associated with frontal injury is somewhat different. A problem-box involving a single ma-

noeuvre such as pulling a rope or turning a crank is solved as effectively after ablation of the frontal areas as before. More complex problem-boxes, involving a series of acts such as the undoing of a latch, pulling a rope and turning a crank, in that sequence, may be negotiated after operation, but mistakes are more numerous and attempts are frequently made to reverse the essential serial order of the acts. The more complex problem-boxes also demonstrate the increased restlessness and distractibility of the frontal area preparation.

Stick-and-platform problem (Jacobsen, Wolf and Jackson, 1935). A chimpanzee is led into a cage, and food is placed on a small platform just beyond its reach outside the cage; if a stick of appropriate length is made available on the platform, a normal animal quickly learns to use the stick to gain the food. The problem may be further complicated by using a series of short sticks to draw in a longer stick, the longest of which is only just adequate to obtain the food. These problems are also readily solved by a normal chimpanzee and by chimpanzees whose frontal areas have been removed from one side.

The situation was quite different when a second platform was introduced, the sticks being placed on one, and the food out of reach on the other, so that the sticks had to be carried from one platform to the next. The problems were so arranged that the animal needed to carry No. 1 short stick from platform A to B, and there rake in the longer No. 2 stick which could be used to secure a longer stick, etc., until a fourth or fifth had been drawn in, each time from an opposite platform and ending on a platform opposite from the food. The two-platform situation thus introduced a new factor, namely, that of "recall" — the essential cues not being in the visual horizon, and *solution of the problem required brief memory of recent sensory experiences*. Removal of the frontal area from one side did not impair a chimpanzee's capacity to solve such problems, but after bilateral removal the failure was profound.

Delayed reaction test. With the animal behind an open grating, food is placed under one of two cups, and an opaque screen is then lowered between the animal and the test object; after an interval, ranging from a few seconds to several minutes, the screen is lifted, the grating opened, and the animal permitted to choose between the two cups. To select the right one, the animal must remember under which cup the food has been concealed. A normal chimpanzee goes to the correct cup without failure after delays as great as five minutes. Unilateral removal of the

frontal areas does not affect its performance, but bilateral extirpation causes complete inability to respond accurately even after delays as brief as 4 to 5 seconds. The frontal area animal is thus unable to retain for a few seconds the memory of a recent event in the face of other *oncoming sensory experience* (Jacobsen, 1935, 1936).

The marked vulnerability of frontal area monkeys to the distracting influence of constantly impinging stimulation is well demonstrated in the delayed response experiments of Malmö (1942). Normal animals were trained to seek food, after an interval of delay, from one of two boxes. The correct box was indicated by a signal light of short duration given at the beginning of the delay period. When the experiments were conducted under ordinary room illumination, ablation of the frontal areas severely impaired performance of these delayed response tests. However, when the general illumination was reduced so as to make the walls and floor of the cage practically invisible, the frontal area preparation was able to execute the test after considerable delay and with a high degree of accuracy.

The situations in which frontal area deficit is most clearly demonstrated are those in which external stimulus control of behaviour is at a minimum. That this deficit is not an absolute one is shown by Finan's (1939) experiments with the shuttle box-problem and temporal maze, in which the animals are required to respond differentially to the passage of a fixed period of time. These problems have in common with the delayed response experiments a minimal control of behaviour from external sensory cues. In contrast to the failure on delayed response tests, frontal area preparations made satisfactory performances on the temporal problems maze. As yet the critical psychological differences between these several problem situations remain to be determined.

EXPERIMENTAL NEUROSES. One of the striking facts disclosed in Pavlov's (1927, 1928) investigations on conditioned reflexes is that dogs, when attempting to discriminate sounds of similar pitch or objects of approximately the same shape, sometimes "went to pieces," developing all the familiar signs of a conflict neurosis. Similar symptoms have been seen in chimpanzees, although measures have been taken to prevent an extreme neurotic breakdown. The behaviour of one of the subjects may be cited. An adolescent female specimen, affectionate, coöperative and eager to work in the problem situations, proved also to be an emotional animal, greatly upset whenever an error was made in the delayed re-

action or other test. In these circumstances it not infrequently flew into a violent temper tantrum, during which she rolled on the floor, beat the cage, defecated and urinated, and often showed signs of diffuse sympathetic discharge. The training in the delayed reaction test was continued over a period of three weeks, and toward the end of it the temper tantrums became so frequent and coöperation so poor that further testing became almost impossible. Fearing that a complete neurosis would develop, the period of training was stopped for a time and, when taken up once more, with somewhat simpler forms of the delayed reaction tests, it again coöperated, though temper tantrums continued whenever a mistake was made.

After removal of both frontal areas, a profound change occurred; to cite Jacobsen's description(1934):

"The chimpanzee offered the usual friendly greeting, and eagerly ran from its living quarters to the transfer cage, and in turn went promptly to the experimental cage. The usual procedure of baiting the cup and lowering the opaque screen was followed. The chimpanzee did not, however, show its usual excitement, but rather quietly knelt before the cage or walked around. Given an opportunity, it chose between the cups with its customary eagerness and alacrity. However, whenever the animal made a mistake it showed no emotional disturbance, but quietly awaited the loading of the cup for the next trial. The opaque door was again lowered, but without untoward effect, and if the animal failed again it merely continued to play quietly or to pick over its fur. Thus, while the animal repeatedly failed and made a far greater number of errors than it had previously, it was quite impossible to evoke even a suggestion of an experimental neurosis. It was as if the animal had joined the 'happiness cult of the Elder Mischeaux,' and had placed its burdens on the Lord. Objectively the animal failed this test and also the simplified form with only the glass door in operation."

The general behaviour of a frontal area chimpanzee is difficult to describe. One can distinguish them from the normal animal by their restlessness, distractibility, and by a rather fatuous equanimity of spirit which one encounters in a good-natured drunkard, but never in a normal chimpanzee. Removal of the frontal areas, therefore, perhaps on account of reducing its capacity for "recall" and of increasing the importance of immediate sensory cues as determinants of response, profoundly alters its behaviour(Jacobsen, 1936), and, among other things, prevents the appearance of the experimental neuroses in certain more complex and abstract situations.

FRONTAL LOBOTOMY. Moniz(1936), the Portuguese neurosurgeon, has applied Jacobsen's findings concerning experimental neuroses in chimpanzees to the surgical treatment of neuroses and of the major psychoses in man. Through burr holes over the frontal areas a "leucotome" is inserted(a hollow needle with a long

stylette which may be caused to bulge through a lateral aperture) and on rotation severs the projections from the frontal area (motor and sensory) before they reach the internal capsule. Unilateral frontal lobotomies of this type are without effect, but bilateral procedures cause conspicuous alterations in the intellectual status of the individual, in some instances a change from profound depression to carefree euphoria.

The procedure has aroused much discussion, principally since 1938, when the previous paragraph was written. Since then, Freeman and Watts (1942) have published their important monograph *Psychosurgery*, and Löwenbach and Stainbrook (1942) and others have published reports on electric shock therapy directed toward the frontal areas. Bilateral interruption of frontal area projections (lobotomy) or electrical "ablation" by high frequency currents have yielded clinical results wholly consonant with the results of animal experimentation. Many of Freeman and Watts' depressed patients have, through frontal lobotomy, been sufficiently improved to warrant return from an institution back to friends and family. In milder cases treated by Löwenbach there have been many instances of complete restoration. There is no doubt that the frontal areas in normal human beings make possible anticipation of the future and in certain pathological situations these same areas precipitate worry and apprehension. Anxiety states which stem from apprehension can be relieved by functional ablation of the frontal areas (Löwenbach) or by actual anatomical interruption of their projections (Freeman and Watts). The usefulness of the less drastic procedure of Löwenbach is receiving wide recognition and deserves further study, both in man and animals (see also Rylander, 1939; Alexander and Löwenbach, 1942; Hutton, 1943).

LOCALIZATION WITHIN FRONTAL AREAS. Jacobsen, *et al.* (unpublished), have studied the effects of subtotal and discrete regional ablation of the frontal association areas in attempting to discover what part of the large cerebral mass is responsible for disturbances in the delayed reaction situation. He finds that lesions corresponding with area 8 or 9 (fig. 102) are without effect on delayed reaction, but that a full-blown deficit can be demonstrated after bilateral ablations of the frontal poles, *i.e.*, areas 9b and 10 (fig. 102). As yet no evidence of functional localization has been found for areas 11 and 12.

CLINICAL STUDIES

SPEECH AREAS. The physiology of the areas concerned in the integration of articulate speech must necessarily be based upon evidence derived from clinical sources. The region commonly designated as the motor speech centre lies in the third left frontal convolution in the region of "Broca's area" (areas 44 and 45, fig. 102), which is no doubt an elaboration of the "premotor area" for the face representation (areas 4c and 6a). Tumours or other lesions restricted to this cytoarchitectural field in a right-handed person cause, in a majority of instances, motor

disturbance in speech mechanism, referred to as "motor aphasia." With it, however, is often found evidence of mental confusion; classical cases of pure motor aphasia are said to retain the capacity to write or otherwise to signal desires but their speech is generally restricted to a few expletives (see Goldstein, 1942).

SYNDROME OF FRONTAL AREAS. Clinical studies indicate that behavioural disturbances are prominent following frontal area lesions in human beings, and nearly all writers on the subject are agreed that remote memory is less impaired by a frontal lesion than recent memory (Goldstein, 1936; Kahn and Thompson, 1934). In the case of bilateral frontal lobectomy, recently studied to great advantage by Brickner (1936), the outstanding features were boastfulness, self-aggrandizement, distractibility and a certain curious hostility toward family and friends. Remote memory of major events was very little impaired, but recent memory was variable and faulty. Orientation in space was reasonably good, but the patient was entirely vague concerning the date of week and month, and he seldom could recall events of a few days past; memories of childhood, however, were unaffected. The man was quite incapable of logical thinking and went off on tangents whenever a topic requiring sustained and simple logical analysis was brought up for consideration.

Though the gap between man and the higher anthropoids is large, it is probable that the basis for these behaviour disturbances lies in the more simple types of deficit found in the higher apes. The deterioration of intelligence in a chimpanzee after removal of the frontal areas does not affect simple learning processes or the retention of simple problem-box and visual discrimination habits, but the difficulties lie in reproductive memory ("recall") as opposed to associative memory. Recent sensory experience is not retained and the animal tends, as it were, to live in a perpetual present with no capacity to adapt future behaviour to immediately past experience. With food out of sight, it is also out of mind, the animal cannot recall where it was seen.

It is significant furthermore that *subtotal* extirpation of the frontal association areas reduced the length of memory span without abolishing the function completely. Other areas of the cortex have been studied to determine whether these defects of recent memory are peculiar to frontal association areas; it has been found that removal of premotor, motor, parietal and temporal lobes have no such effect on recent memory (Jacobsen, 1934; Jacobsen and Elder, 1936).

Many other cases of frontal lobe injury in man have been studied in detail by Goldstein(1936), and it is clear that the basic disturbances which he describes as characteristic of bilateral destruction of the frontal areas are similar to those described by Jacobsen in subhuman primates. The similarities will no doubt become even more evident when a common terminology has been adopted by the clinical and the experimental laboratories.

SUMMARY

The frontal areas include all the isocortex lying rostral to the premotor and eye fields(areas 6 and 8); in Brodmann's map of the monkey they are designated areas 9, 10, 11 and 12. In man Broca's area (area 45) which is concerned with articulate speech is to be separated from the frontal areas, since it represents a special elaboration of the premotor face area. The recent work of Walker(see fig. 102) indicates that areas 13 and 14(orbital surface) and areas 24 and 25(medial surface) should also be grouped with the frontal areas.

The frontal areas are inexcitable to all forms of electrical stimulation and their primary ablation has little if any effect upon reflexes or posture of the extremities in any primate form including man. When removed *after* ablation of motor or premotor areas any existing postural and reflex changes tend to be accentuated.

Unilateral ablation of areas 9, 10, 11 and 12 causes no obvious behavioural disturbance in monkey, chimpanzee or man; but their *bilateral* destruction leads to a conspicuous syndrome characterized in animals by restlessness, distractibility and failure of immediate memory(delayed reaction test). A parallel syndrome occurs in man, and in man the behavioural aberrations are more readily analyzed.

XXIII

CEREBRAL CORTEX: AUTONOMIC REPRESENTATION

HISTORICAL NOTE

Soon after the discovery of the motor area Schiff(1875)and Danilewsky(1875) found independently that the heart rate could be increased by electrical stimulation of the frontal lobes. Others soon recorded the effects of such stimulation upon the blood pressure level(Bochfontaine, 1876; Cerevkov, 1892); faradic stimulation of the frontal lobes caused conspicuous elevation of the systolic blood pressure of curarized animals, and Stricker(1886), on the basis of these and further experiments of his own, postulated the existence within the cerebral cortex of vasomotor centres. The name of Hughlings Jackson has been mentioned in connection with many early studies upon the functions of the cerebral cortex; from his studies of epilepsy he had concluded as early as 1876 that visceral functions must have extensive representation in the cerebral cortex. He had observed and frequently stressed the fact that these functions were often grossly disturbed during epileptic seizures which obviously had their origin at the cortical level. Bechterew and Mislawski(1886)reported slowing and acceleration of the pulse on stimulation of the cerebral hemispheres, and in curarized cats and dogs they obtained rises and falls of blood pressure from points on the anterior and posterior sigmoid gyri. These findings were confirmed by Cerevkov in 1892. Winkler in 1898 also detected acceleration of the pulse on stimulating the dog's frontal lobes, but he did not record the blood pressure. In 1899 Howell and Austin reported in animals anesthetized with morphia and ether that a fall of blood pressure generally resulted from stimulation of the sigmoid area(dogs); but, if morphia and curare were used, the effect was usually a rise of pressure. Later work indicated that there was sometimes a rise, sometimes a fall of blood pressure from closely adjacent foci, even with the same anesthetic and similar stimulation. Other instances of opposed autonomic effects from different foci of the cerebral cortex have been frequently recorded. In experiments published in 1906 and 1910, E. Weber recorded changes in limb and organ volumes following stimulation of the cortex in dogs. In 1924 Dusser de Barenne and Kleinknecht found both pressor and depressor points with a strength of stimulation that caused only slight motor effects(dogs, cats, and rabbits). Recent surveys of the older contributions are found in the reviews of Spiegel(1928), Karplus(1937), Kennard(1936, 1937; in Bucy, 1943), E. C. Hoff(1940), Miller(1942)and Gellhorn(1943).

THE concept of levels of functional activity has been widely applied in relation to the somatic division of the nervous system; Hughlings Jackson(1875), who was largely responsible for formulating the hypothesis, was the first to appreciate that "visceral function," as he termed it, must also be regulated at different levels of increasing complexity, including

the highest cortical level. Although the autonomic system by definition has been regarded as a peripheral system (Langley, 1921), it was early recognized that the spinal cord, medulla and also the hypothalamus play an important part in regulating autonomic functions; and, as indicated above, the relation of the cerebral cortex to these functions has been frequently discussed, but appreciation of the extent of its influence has become obvious only within the last few years. The more recent experimental studies bearing upon the question may be summarized under the headings of stimulation and ablation.

EXPERIMENTAL STUDIES

Electrical stimulation by induced currents, or condenser discharges, has given clear cut evidence of vasomotor, gastrointestinal, and of many other forms of autonomic representation within the cerebral cortex. The motor regions of the autonomic system intermingle with those of the somatic motor areas, and in monkeys are largely restricted to the agranular frontal cortex, though facilitated responses may be obtained from area 9 as well as from 3-1-2. Autonomic responses of the intrinsic eye muscles have been obtained from areas 8 and 19. The cardiovascular, sudomotor, ocular, gastrointestinal, and various other autonomic effects will be discussed in this order.

CARDIOVASCULAR SYSTEM. Faradic stimulation of certain regions of the cerebral cortex evokes cardiovascular reactions of a pronounced character. Thus weak faradic stimulation of areas 4 and 6 in cat or monkey under ether anesthesia may evoke, after a latency of 2 to 15 secs., primary elevation in systolic blood pressure of as much as 80 to 110 mm. of mercury (fig. 103). In the monkey and chimpanzee rises were somewhat less marked, but were nevertheless easily obtained (Hoff and Green, 1936).

That these reactions were purely cortical responses was proved by the following control observations (Hoff and Green): (i) they disappeared when the anesthesia became deep; (ii) application of a local anesthetic to the excitable focus abolished the response, but it recurred if the stimulating electrode was plunged several mm. into the cortex thus penetrating beyond the region of local anesthesia (fig. 103); (iii) the response disappeared when the cortex was so undercut that the anatomical projections from the excited region were destroyed; (iv) that the responses were not due to spread of stimulation was also assured by the fact that they could be obtained with an intensity of stimulus insufficient to cause movements of the skeletal muscles in non-curarized animals; (v) finally, discrete points were disclosed often in close proximity to the pressor points from which fall of the

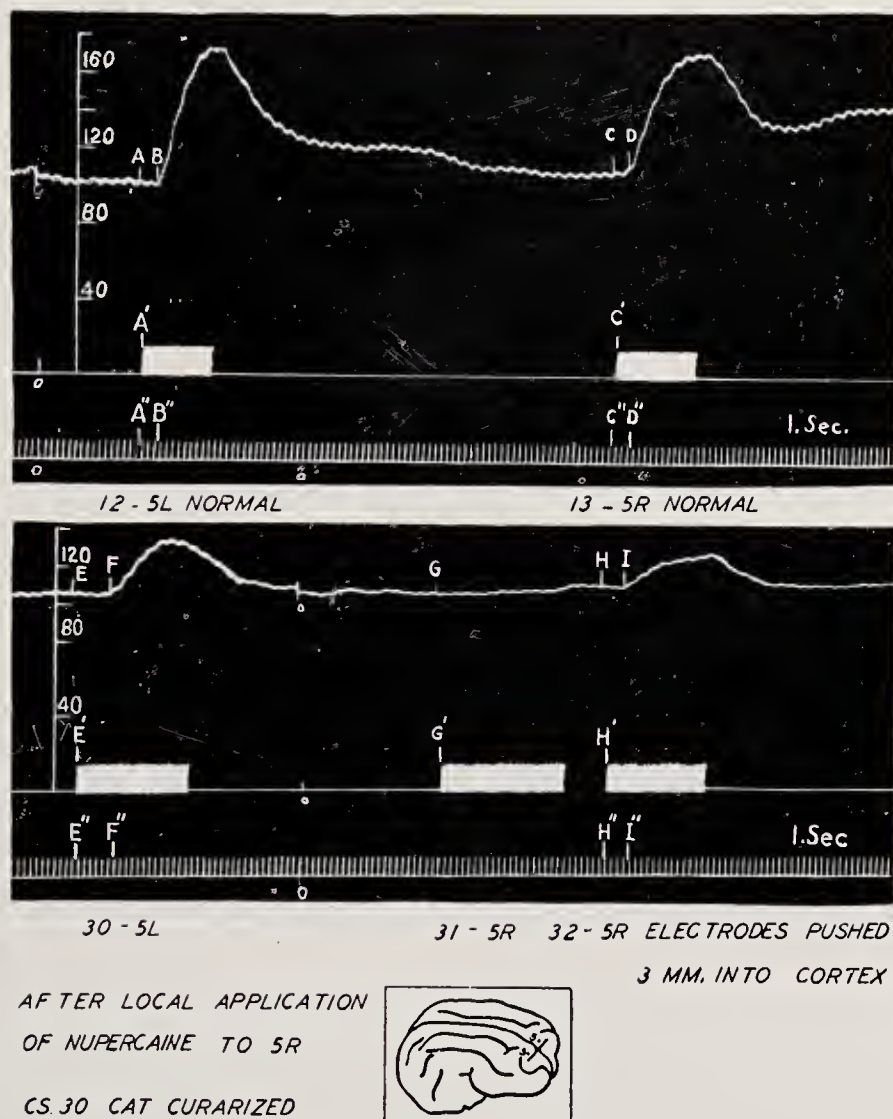


FIG. 103. Showing responses of blood pressure to stimulation of frontal lobe of curarized cat. Above are normal responses. Below after application of nupercaine to excitable focus, one response is diminished and in middle completely abolished. When electrodes are thrust into cortex the response returns (Green and Hoff, 1937).

blood pressure resulted. No study of the adequate stimuli essential for evoking these vasomotor effects has yet been made. Slow rates of stimulation are more effective than rapid, and while faradic stimuli are effective the optimal current pulse has not been determined.

On investigating the peripheral pathways, it was found that section of the splanchnic nerve diminished but did not abolish the pressor re-

sponse from the cortex. Simultaneous section of the splanchnic and ablation of the stellate ganglia on both sides further diminished, but again did not wholly destroy the reaction. Section of the vagus nerve considerably facilitated the response. Crouch and Thompson(1939)also located vasopressor foci near the motor area of cats and dogs from which elevations of pressure were consistently obtained on faradic stimulation. The *depressor* points were often closely adjacent to the pressor areas; in some instances on stimulation of depressor regions, falls of systolic pressure of 10 to 20 mm. occurred after a latency of 3 to 10 secs. (Carlson, Gellhorn and Darrow, 1941). Hsu, Hwang and Chu(1942) have reported that electrical stimulation of focal motor points in the cortex of dogs under chloralose anesthesia gives predominantly depressor effects. This drop of blood pressure is not influenced or abolished by section of both vagi. In these experiments, the renal volume is always increased during the fall in blood pressure.

Turning to the *heart rate*, excitation of pressor foci caused an acceleration of approximately 10 per cent during the rise of arterial pressure; during the fall of pressure, however, the heart rate became retarded as much as 50 per cent. This proved true both in lightly etherized animals and curarized preparations(Hoff and Green, 1936), but the slowing of the pulse did not occur after vagotomy. It has proved easier to demonstrate primary slowing of the heart from cortical stimulation in preparations deprived of the stellate ganglia and adrenal glands. In monkeys changes of heart rate as great as 50 per cent were observed. Under curare, which affects the endings of the vagus nerve, primary slowing of the heart was less conspicuous.

From these observations it is clear that the cerebral cortex contains both sympathetic and parasympathetic representation. Hence, when the vagus and sympathetic are both intact, the effects of stimulation are probably never pure but rather an algebraical summation mediated by two opposing systems of nerves.

Peripheral vasomotor effects. If changes of blood pressure are obtained on stimulating the cortex, one assumes that they are brought about by altering the peripheral resistance, *i.e.*, by constriction or dilatation of the arteriolar and capillary beds. The earliest experimental analysis of the question is that of Eulenburg and Landois(1876), who recorded that stimulation of the motor areas gave rise to noticeable

cooling of the opposite side of the body, and they concluded that the motor region of the cortex directly regulates the vasoconstrictors of the opposite side of the body. Later investigators, repeating the observations of Eulenburg and Landois, found evidence both of vasoconstriction and of vasodilatation, depending upon the region of the cortex stimulated — a point entirely in keeping with the differing effects on the blood pressure of adjacent foci. Experiments of Green and Hoff(1937), in which limb and renal volumes were simultaneously recorded in cats and monkeys, showed that stimulation of the cerebral cortex causes diminution of kidney volume accompanied by a simultaneous increase in limb volume. This indicates that the cerebral cortex is capable of initiating a direct shift of blood from the visceral to the muscular bed. Since dilatation still occurred to approximately the same extent after the skin from the extremity had been removed, the changes in limb volume were due primarily to an increased vascular supply of the muscles. Denervation of the limb abolished the response, which proved that the effect was mediated by nervous pathways and not by humoral agents released into the circulation.

These reactions were also most readily obtained from areas 4 and 6. Evidently, therefore, there exist in the cortex autonomic mechanisms capable of augmenting the blood supply of muscles which are thrown into activity, and regulation does not depend entirely upon secondary metabolic changes in the muscle itself(*e.g.*, dilatation of capillaries from accumulation of acids or other metabolites).

Effects of ablation. Disturbances in the autonomic sphere were early described in clinical cases of injury of the cerebral hemisphere or its projections. Thus in 1867 Chevallier mentioned that cases of hemiplegia exhibited elevations of temperature of from 2 to 11 degrees in the affected extremities. In certain cases of hemiplegia Vulpian(1875)reported edematous swelling. Gowers(1886)found that whereas *acute* cases of hemiplegia generally have warm extremities, *chronic* cases are likely to exhibit a lower temperature on the affected side. From the observations of Peritz(1915), Kahler(1922), Berger(1923)and Kennard(1937; in Bucy, 1943), one may assume that some degree of vasomotor disturbance invariably accompanies hemiplegias of capsular or cortical origin which cannot be attributed entirely to disuse(Bucy, 1935); whether the affected extremities exhibit a higher or lower temperature

than those on the normal side depends in part on the duration of the lesion, and on the temperature and humidity of the environment(Hitzig, 1876).*

An experimental approach to the problem has been made by Pinkston, Bard and Rioch(1934; Pinkston and Rioch, 1938)and by Kennard (1935). In dogs a lesion of the motor area is generally followed by dilatation in the corresponding extremity rather than constriction, indicating that the dominant vasomotor representation in this part of the dog's cortex is evidently constrictor. When the animal is exposed to heat after the whole cortex is removed, the body temperature rises considerably before the mechanisms of heat loss, such as panting and perspiration, are activated(ch. xiii). These important studies may be summarized in the author's words:

"After removal of the neopallium and part of the hippocampus, including the fornix, with subsequent secondary degeneration of large portions of the dorsal thalamus, the dogs showed the following functional changes in their temperature-control mechanisms: 1, chronic vasodilatation, with failure of the skin vessels to constrict normally to cold; 2, absence of true polypneic panting; 3, a very delayed slow type of hyperpnea in response to conditions that promptly induced true panting in the same animals before operation; 4, a rise in rectal temperature before hyperpnea developed; 5, immediate and vigorous shivering in response to cold, frequently producing a rise in body temperature, whereas before operation the same animals showed the usual delayed and less marked reaction with a fall in body temperature.

"The cats with equivalent lesions behaved in a similar manner in response to cold. The responses, however, were subject to wider variations than those of the dogs. There were no differences in temperature control noted between these animals and others with more extensive lesions, which left only the hypothalamus intact, together with the contiguous portions of the medial basal olfactory areas and of the caudal pole of the dorsal thalamus"(Pinkston, Bard and Rioch, 1934).

The experiments of Pinkston, *et al.*, thus clearly establish that the cerebral cortex, by virtue of its regulatory action on the autonomic system, is an essential part of the bodily mechanism of heat regulation(see ch. xiii). In harmony with this Kennard(1935)found following ablation of area 4 of monkeys, that the opposite extremities become slightly cooler than the normal. A much more marked effect was seen when the premotor region was removed, for such an animal exhibited for several weeks complete paralysis of its mechanism for reflex vasodilatation and, placed in a warm atmosphere, the normal extremities quickly

* Three striking cases of hemi-edema following hemiplegia have recently been reported by Friedman(1942).

dilated and the animal lost heat through these surfaces, whereas the paretic extremities exhibited no such reflex adjustment and the temperature remained considerably cooler than on the normal side. Pinkston and Rioch(1938) have obtained the same result in monkeys.

SWEATING. Disturbances of sweat secretion occur in clinical lesions of the frontal lobes and internal capsule(Bikeles and Gerstman, 1915), having been early observed by Gowers(1886)and recently studied in detail by Guttmann and List(1928). The latter authors found consistently that augmentation of sweat secretion(hemihyperhydrosis)occurs on the side opposite lesions of the "agranular" frontal cortex or the internal capsule. There appears, however, to be no clear relation between the severity of the sweating and the degree of paralysis. They were unable to decide whether the hyperhydrosis resulted from irritation of the cortex or was a release phenomenon due to removal of inhibition. Excessive sweat secretion in epileptic seizures has been observed by Toporkoff(1925)who described a Jacksonian seizure which commenced with profuse hyperhydrosis, localized in the right hand and elbow.

Experimental studies of the problem have been made by Winkler (1908), List(1936)and many others. The most fruitful results have undoubtedly been obtained by application of the technique of the "psychogalvanic" reflex, *i.e.*, measurement of skin resistance. Darrow(1937 a&b; 1942)has shown that there is a close correspondence between the activity of the sweat glands and the galvanic skin response. Local vasomotor changes may also affect the galvanic skin response, but the activity of the sweat glands is by far the most important factor. In 1930 Langworthy and Richter, and Wang and Lu observed that stimulation of the region of the cat's motor area gave rise to a conspicuous drop in skin resistance(footpads), the effect being most marked contralaterally. They carefully explored the entire surface of the cortex and could locate only two active foci, one lying in area 6 and the other in the anterior part of the temporal lobe. They followed the pathway from which the reaction could be obtained, and concluded that two tracts conveyed the effect — the frontopontine and a temporopontine fasciculus, *i.e.*, the tracts were independent of the pyramidal pathway, since both passed in the internal capsule, and in the peduncle responses were obtained from the regions of the frontopontine and temporopontine projections rather than from that of the major corticospinal projections. Wang and Lu studied the frontopontine projections and their results agree with those

of Langworthy and Richter. They also observed, as had Langworthy and Richter, that similar effects on sweat secretion could be obtained from the hypothalamus, but that the hypothalamus could be destroyed without abolishing the response from the cortex. They concluded that the response from the two regions was mediated by different (extrapyramidal) pathways.

Striking confirmation of these studies has come from the work of Schwartz (1937) who ablated foci corresponding with Langworthy and Richter's frontal area (in cats). Schwartz points out that various stimuli, auditory and cutaneous (pencil tap, whistle, pinching of back, etc.) cause a prompt fall in resistance of the footpads due to reflex activation of the sweat glands. This is the familiar "psychogalvanic" reflex, which he distinguishes from the "segmental" galvanic reflex obtained by pinching the skin of the extremity from which the record is taken. The psychogalvanic reflex is completely abolished by removal of the cerebral cortex. The segmental galvanic reflex, on the other hand, depends only upon spinal and medullary pathways and is present in the decerebrate animal. Schwartz attempted to determine what part of the cerebral cortex is responsible for the integration of the psychogalvanic reaction. In cats from which all parts of the cerebral cortex, except area 6, were removed, the reaction was normal. If area 6 was ablated and all the rest of the cortex allowed to remain intact, the response was abolished on the side opposite to the lesion, but was preserved on the ipsilateral side. He concludes that the premotor region (area 6) is the excitatory center essential for the psychogalvanic reflex.

PILOMOTOR EFFECTS. As with the galvanic reaction, there are also two types of pilomotor reaction, one affected by cortical lesions and the other not. This has been brought out by Brickner (1930), who points out that the segmental pilomotor reaction is a low order reflex mediated "through a simple reflex arc, segmentally and without the involvement of any long ascending or descending tracts within the nervous system." The other is the pilomotor response to an emotional stimulus. In cases of hemiplegia the segmental pilomotor reactions discussed by André-Thomas (1921) and others are essentially unaffected, but the emotional pilomotor reactions are grossly exaggerated on the hemiplegic side and are seldom present on the unaffected side. Böwing (1923) reports similar augmentation of pilomotor response on the paralyzed side in 8 of a series of 15 hemiplegics. André-Thomas failed to obtain pilomotor re-

actions in cases of parietal lobe lesions when the affected extremities were stimulated. Kennard and others(unpublished)found exaggerated pilomotor reactions, following bilateral ablation of the premotor cortex of monkeys. Langworthy and Richter(1933)studied the pilomotor reactions which exist *par excellence* in the porcupine, and found it impossible to evoke them by cortical stimulation, but that they were readily evoked on stimulating the anterior colliculi. When small lesions are made in the posterior colliculus, response is abolished, the abolition being particularly striking with lesions in this area in primates(Walker, 1940b). Pilomotor effects are of some interest because in hairy animals they play a part in heat regulation(ch. xiii). Lindsley and Sassaman (1938)have studied the EEG of a human being capable of voluntary piloerection and found that the premotor areas showed EEG changes during the volitional activation.

OCULAR EFFECTS. Sympathetic and parasympathetic innervations of the intrinsic eye muscles are also influenced from the cortical level. Parsons (1901)made a study of the pupil dilator centres in the cortex finding that dilator effects from the region of area 8 are diminished but not abolished by section of the cervical sympathetic(Karplus and Kreidl, 1910). Constrictor effects are also obtainable from the cortex. In chapter xxi, reference has already been made to Barris' pupillary constrictor centre in area 19 which Dowman(unpublished)has confirmed in the monkey; Barris(1936)traced the fibre connections from this area to nuclei in the tegmentum. Further studies on these anatomical connections have recently been made by Hare, Magoun and Ranson(1935). The effects of ablation have been discussed in chapter xxi(see Ury and Oldberg, 1940).

The work of Morison and Rioch(1937)indicates that nictitating membrane of cats can be directly excited from the part of the frontal lobes evidently corresponding with area 8. Reactions of the nictitating membrane evoked from stimulation of the sciatic nerve could also be inhibited from stimulation of points just rostral to the anterior sigmoid.

GASTROINTESTINAL REPRESENTATION. Attention has often been drawn to the fact that epileptic seizures emanating from the cortical level frequently begin with a "gastrointestinal aura," *i.e.*, with gastric sensory impressions and motor action of the stomach and intestines. Experimental analysis of the problem began with Bochefontaine(1876).

Stimulation. Bochefontaine observed that electric stimulation of the

dog's sigmoid gyrus caused contraction of the stomach, especially near the pylorus, but the pyloric sphincter itself was relaxed and there was usually increase in peristaltic movements of the small intestine and colon. The observations were confirmed by Hlasko(1887) and Bechterew(1911, vol. 3). With dogs under curare Bechterew observed that faradization:(i)of the anterior part of the sigmoid gyrus caused slowing of the rhythmic pyloric movements of the stomach with increase in general contraction of the walls;(ii)of the posterior part of the sigmoid gyrus gave active rhythmic movements of the pylorus;(iii)and occasionally from the region just lateral to these two areas there were primary movements of the cardia. Bechterew concluded that the cortex contained centres for excitation and inhibition both of the pylorus and stomach walls, possibly also of the cardia. He also obtained increased peristaltic movements of the small intestine with similar stimulation. Page May(1904)failed to confirm many of these observations and attributed the effect to the escape of stimulating current; the work accordingly was largely put aside.

Cushing's(1932)emphasis upon the relation of cerebral trauma to the gastrointestinal tract(ch. xiii)has caused the problem to be studied afresh within the last few years. Watts and Fulton(1935)observed changes in intestinal movement of monkeys under light ether anesthesia on stimulating various parts of the frontal lobes, the more excitable foci being in area 6. Beattie and Sheehan(1934)had observed changes in gastrointestinal movements from stimulation of the hypothalamus of monkeys(ch. xiii), and Sheehan(1934)described marked inhibition in peristaltic movements of *recently fed* monkeys when area 6 was stimulated, but there was little response of a definite character from the quiescent unfed stomach; from stimulation of area 13(fig. 102)much more conspicuous inhibitory effects can be obtained on the gastric musculature(Bailey and Sweet, 1940).

Ablation. There is also a large body of evidence indicating that frontal lobe lesions, especially when bilateral, cause disturbances of motility and possibly also of secretion of the gastrointestinal tract. Watts and Fulton(1934)have described three instances in which monkeys developed acute intussusception with fatal obstruction following bilateral ablations of the frontal lobes(or its parts). When intussusception does not occur, such animals are prone to become ravenously hungry, eating an abnormal quantity of food, and sometimes passing undigested food in

their feces. Unpublished studies of Messimy and Clifton in which the gastrointestinal movements were studied by X-ray and by measurement of the rate of transit of carmin before and after bilateral ablation of the frontal association areas, indicate that the motility is moderately increased (rate of transit of carmin augmented) following such lesions. The effects, however, tend to pass off with time. Evidence of morbid hunger is more marked in animals with premotor ablation than in those with ablations restricted to areas 9, 10, 11 and 12 (see Hesser, Langworthy and Kolb, 1941).

Bilateral ablation of the frontal lobes caused marked hyperactivity of the stomach, sometimes accompanied by pyloric spasm, lasting several days after the procedure. Complete removal of one or both cerebral hemispheres was followed by similar but more intense disturbance of motility. Ablations of the occipital lobes, even if bilateral, caused no appreciable change in gastrointestinal movements. In some animals, erosions of the gastric mucosa were noted at autopsy. Mettler and his co-workers (1936) conclude that "ulceration is only one phase of a much more extensive disturbance of the gastro-intestinal tract due to autonomic imbalance."

The clinical implications of these and earlier studies have been discussed by Watts and Frazier (1935). The gastrointestinal aura, which occurs in cases of localized epilepsy, coincides with vigorous and abnormal gastrointestinal movements; they are initiated focally in the cortex by the irritating agent responsible for the subsequent epileptic seizure. The existence within the cerebral cortex of gastrointestinal representation thus gives a rational basis not only for the gastrointestinal aura of epilepsy, but also for the large number of gastrointestinal disturbances known to accompany states of anxiety, unusual mental activity, etc. Little is yet known concerning the influence of the cortex on gastrointestinal secretion, but it may be pointed out that the "psychic" flow of gastric juice studied for so many years by Pavlov (1927) depends upon the integrity of the cerebral cortex. Conditioned-reflex salivation also depends upon the cortex, probably upon area 6a (lower part).

Morbid hunger (bulimia). Cases of morbid hunger following accidental lesions of the brain have been described sporadically in the literature. They were discussed by Bechterew (1911), and they were made the subject of a detailed paper by Stephen Paget (1897). One of the cases referred to by Bechterew was that of a child who

suffered a depressed fracture in the mid-frontal region from the kick of a horse. When the child recovered consciousness, he cried constantly that he wanted more food. The splinters of bone which compressed the frontal lobe were removed surgically and four days thereafter the symptoms of abnormal hunger ceased. Another case, from Paget's series, was that of a young woman 24 years old who was knocked down and fell striking her head on a step; she had concussion with vomiting followed by fever which lasted about a week. She then began to have a voracious appetite so that she would not leave the house even to go a short distance without taking a supply of food in her pocket. This abnormal hunger lasted for about three months, varying from time to time in its intensity. Pathological hunger is also encountered in Pick's disease in which bilateral degeneration of the frontal lobes occurs. The ravenous hunger of certain idiots and general paretics is also well recognized in psychiatric institutions and schizophrenics are likely to pass through a period of polyphagia some time in the course of their disease. Unfortunately the gastrointestinal motility of these cases has not been studied. P. Levin (1936a) reports increased gastrointestinal motility in a group of children with cortical diplegia who also showed morbid hunger. M. Levin (1936) has described an interesting new syndrome of periodic somnolence and morbid hunger due possibly to cortico-hypothalamic derangement. It seems probable that involvement of the orbital surface of the frontal lobe is responsible for bulimia.

OTHER AUTONOMIC FUNCTIONS. In his review on the cerebral regulation of autonomic functions Spiegel (1928) pointed out that there is a close topographical relation between the cortical areas from which certain autonomic organs can be activated, and the cortical foci which excite the adjacent somatic structures. Thus it has already been stressed that pupillary dilatation (sympathetic nervous system) is obtained from foci closely adjacent to, and probably overlapping with, the parts of area 8 which give eye movements (ch. XXI). From the same region Bechterew and Mislowski (1891) evoked *lacrimation*, a parasympathetic reaction. Lacrimation has also been induced by others in stimulating the eye fields.

Similar overlapping of representation of somatic and autonomic representation has been observed in the case of *salivation*. Bechterew (1911) described a sharply localized focus from which active salivation was obtained; and from the same, or closely adjacent foci, movements of tongue and face could be evoked. Similar observations have been made in monkeys (Walker and Green, 1938; Wang, 1943).

Another case in point is that of *micturition*. Here is a complicated neurological mechanism involving somatically innervated sphincters and an autonomically innervated viscus. The human infant learns in the course of development to inhibit the subcortical reflex of bladder evacuation; but with this also develops the power voluntarily to initiate

the act. Bilateral lesions involving parts of areas 4 and 6 lying on the medial surface of the hemisphere cause loss of volitional control over the bladder reflexes, and urinary incontinence ensues. How much of this control is due to the corticospinal tract itself, and how much to the extrapyramidal projections to subcortical centres has not yet been determined. Langworthy, *et al.*(1940), point out that cortical lesions, especially when bilateral, cause signs of release of the bladder reflexes with increase in the response to stretch — hence the phrase “spastic bladder.” In man the “spasticity” manifests itself in urgency, limited capacity, and violent contraction when the bladder is rapidly filled. In cats Langworthy and Kolb(1933)observe that stimulation of the premotor area caused changes in bladder pressure. When the pressure was high, such stimulation might cause a fall in pressure; when the pressure was low, elevation could be produced after a considerable latency. The stretch reflexes of the bladder are similarly responsible for its evacuation in spinal man. Watts and Uhle(1935)studied the problem in clinical cases of brain tumour, confirming the observations of Langworthy and his colleagues on hyperexcitable bladders. They also found hypotonic bladders but were unable to localize the areas responsible for the two forms of disturbance(ch. viii).

Respiratory movements are also influenced at the cortical level, as pointed out in chapter xxi, but such movements involve primarily somatic reflex mechanisms.

DISCUSSION

LEVELS OF FUNCTION. The concept of levels of function is nowhere better illustrated than in the autonomic nervous system. As in the somatic sphere, *intersegmental* reflexes occur involving autonomic pathways. A classical example of such segmental reactions is the reflex of vasodilatation which occurs in the other three extremities when one extremity is placed in hot water. This reaction has been studied in detail by Lewis and Pickering(1931)and by Uprus, *et al.*(1935). The reaction occurs in the decerebrate animal and possibly also in the high spinal preparation. It is a basic segmental reaction similar to the flexion reflex of the somatic system; though it may be affected by higher levels of integration, it is clearly not dependent upon them, and the presence of these reactions in cases of hemiplegia need not be evidence against autonomic representation in the cortex.

But there are also *suprasegmental* levels of integration of varying degrees of complexity in the autonomic system. The medulla oblongata maintains the blood pressure at a fairly constant level, whereas in the spinal preparation blood pressure regulation is imperfect and the level fluctuates (ch. x). Galvanic reflexes (sweating) are also integrated at the medullary level (Darrow, 1937).

At the *hypothalamic* level, more complex autonomic functions are integrated, notably those concerned with heat regulation, which involve many different peripheral mechanisms, principally autonomic, but partly somatic (panting and shivering); so one must anticipate at the hypothalamic level some degree of overlapping of somatic and autonomic representation. The *thalamic and striatal* levels have not yet been carefully analyzed from the point of view of autonomic function. However, the early observations of Hale White (1890) and studies on striatal stimulation indicate that the neostriatum plays an important part in the regulation of autonomic function. The precise character of this regulation is not yet determined, but the many disturbances in the autonomic sphere — salivation, hyperhydrosis, lacrimation — which accompany clinical lesions of the striatum strongly suggest its active participation in these functions; and it is clear that the intermingling of somatic and autonomic representation essential for integration is more extensive than at the hypothalamic level.

At the *cortical* level, evidence of overlapping of autonomic and somatic representation is evident throughout the entire motor region of the cortex; others have suggested that there is similar overlapping of visceral and somatic *sensory* representation in the great sensory fields of the cortex. The existence of this dovetailing of representation makes possible an integration and unification of response which is undoubtedly the basis of many of the most fundamental adjustments of the organism. The newer disclosures concerning the cerebral cortex and the autonomic system give an adequate physiological basis for the long-recognized relationship between mental states and visceral processes. To cite two specific examples, the work of Green and Hoff (1937) indicates that activation of areas 4 and 6 may cause a direct shift of the blood from the visceral to the muscular bed, the reaction occurring even though the muscles themselves are prevented by curare from somatic movement. Undoubtedly the same impulse-pattern which throws the muscle into contraction also diverts an appropriate amount of blood

into the muscle bed. As another example, Darrow(1937), in his study of the sweat glands, points out that the skin exhibits an exquisitely delicate responsiveness to mental states as well as to physical work, anticipated or actual. Thus when the limb reaches for an object the sweat glands are activated prior to the time the object is actually grasped; palmar perspiration is functionally valuable for the improvement of tactual acuity and grip upon objects, and is called forth in situations demanding delicate tactile discrimination. Darrow has also studied the influence of emotion, sleep, states of anxiety and mental tension upon the skin, and has found correlations that would be quite impossible to explain on any assumption other than that the reactions are actually inaugurated and controlled by the cortex.

ANATOMICAL PATHWAYS. There is still some uncertainty about the precise anatomical pathways involved in the mediation of autonomic regulation by the cerebral cortex. The first to investigate the problem experimentally were Karplus and Kreidl(1910), who found that the pupillary dilator response from the cerebral cortex of cats was abolished on destruction of the hypothalamus. They concluded, therefore, that the reaction depended upon an anatomical pathway which passed from the cortex via the hypothalamic nuclei. Similar studies of the galvanic skin response by Wang and Lu(1930) indicated that this reaction could still be obtained from the cortex after the hypothalamus was destroyed. They, therefore, postulated a direct extrapyramidal cortical pathway which did not involve the hypothalamus. The problem was again taken up in some detail by Hunsicker and Spiegel(1933). They divided their experiments into two parts: in one group, a series of cats were subjected to medullary section of the pyramidal tract; in the other group, the hypothalamus was destroyed. In both groups the motor cortex of the frontal lobes was stimulated and reactions of the pupil, blood vessels, sweat glands and urinary bladder were observed. In both groups cortical stimulation elicited autonomic responses in the organs just mentioned. From this they concluded, as had Wang and Lu, that both the corticospinal pathway and the extrapyramidal projections from the cortex influence autonomic centres of medulla and spinal cord. Some of the extrapyramidal projections may normally act through the hypothalamus; others can act independently of it. If the pyramidal tracts themselves influence autonomic centres of the cord, one must postulate direct or collateral innervation of the lateral column cells in the cord by the corticospinal neurons. Hoff and Hoff(1934) have found bouton degeneration, following injury of area 4, on the lateral columns as well as on internuncial neurons in the intermediate grey.

SUMMARY

The concept of levels of function applies to the autonomic as well as to the somatic division of the central nervous system. Segmental autonomic reflexes are well known, but they are insufficient of themselves to regulate such functions as the level of the blood pressure; for this medullary centres are essential. More complicated functions such as heat regu-

lation are integrated at the hypothalamic level; other and more complex integration takes place at the striatal level. In the cortex there is extensive overlapping between autonomic and somatic motor representation, making possible unified correlation between the reactions of the two systems. In general, the topographical relation between the cortical areas influencing specific autonomic functions is close to the cortical area influencing the corresponding somatic functions. Thus lacrimation is observed on stimulating the eye fields, salivation, on stimulating the motor representation of the face and tongue.

Other autonomic functions regulated at the cortical level are as follows; cardiovascular reactions can be obtained from faradic stimulation of areas 4 and 6, pressor and depressor points seem readily demonstrated, and also foci which influence the heart rate. Since both sympathetic and parasympathetic representation can be demonstrated, the effects of stimulation are necessarily an algebraical summation. To bring out sympathetic representation it is essential to paralyze the parasympathetic outflow and vice versa. Vasoconstriction and vasodilatation of the extremities may also be evoked by stimulating areas 4 and 6.

Gastrointestinal representation has been indicated both by changes in peristaltic activity of stomach and intestines produced by faradic stimulation, and also by disturbances of motility which follow bilateral ablation of the frontal region. In the latter circumstances hypermotility is prone to develop, and associated with it may develop morbid hunger, causing the ingestion of many times the normal amount of food and failure of adequate digestion of the food consumed.

Disturbances of sweat secretion may result from stimulation of area 6. Schwartz' recent study of cats indicates that ablation of area 6 and of no other part of the cortex abolishes the psychogalvanic reflexes(sweating), but not the intersegmental galvanic reflexes. The recent work of Darrow(1942)also indicates that the human skin is exquisitely sensitive to mental reactions of all types, and anticipatory sweating also develops in association with simple volitional movements such as those involved in the simple grasping of an object.

Conditioned reflex salivation and gastric secretion(the psychic secretion of Pavlov)are also dependent upon the integrity of the cerebral cortex.

XXIV

THE EXTRAPYRAMIDAL MOTOR SYSTEM: BASAL GANGLIA

HISTORICAL NOTE

The functions of the basal ganglia have been the source of much speculation since the beginning of anatomical study of the brain.* Willis(1664)suggested that they were "internodes" by which the cerebrum came in rapport with the medulla oblongata. Swedenborg(1740), the great anatomist and religious leader, saw in these basal ganglia the seat of primary sensibility of body and soul, and he added that "all determinations of the will also descend by that road." Experimental study began with Flourens(1824), who mechanically stimulated the basal ganglia of rabbits without result(he failed to obtain movements from similar stimulation of the cerebral cortex). Magendie(1841)also irritated the striatum of the rabbit, finding that progression movements developed when both sides were stimulated simultaneously; similar results were obtained by Nothnagel(1873)with chemical stimulation. Budge(1839)introduced the idea that the striate bodies were concerned with visceral function, recording that intestinal movements were increased when the striatum was probed; and Hale White(1890), investigating along similar lines, observed changes in temperature of the opposite side of the body following striatal lesions.

After the discovery of the motor area, there was renewed interest in stimulating the basal ganglia. Ferrier(1876), for example, recorded contralateral contractions of the skeletal musculature(due probably to escape to the internal capsule), and the question of the excitability of these ganglia is still under discussion. The most notable advances in knowledge of the basal ganglia have come from studies of clinical lesions. Kinnier Wilson(1912)recognized the syndrome of chronic lenticular degeneration and Cécile Vogt(1911a&b, 1920)described a variety of other motor disturbances associated with more specific lesions of the striate complex. The interrelations of these nuclei with other subcortical mechanisms such as those of body of Luys and substantia nigra have recently formed the chief subject of discussion of the Association for Research in Nervous and Mental Disease(December, 1940)and the volume of *Research Publications*(published in 1942)gives valuable source material on recent developments. See also the excellent reviews of Rioch(1940)and Bucy(1942).

* There is much confusion in terminology of the so-called basal ganglia. Originally they comprised all subcortical ganglia of the forebrain including the thalamus; current usage excludes thalamic and hypothalamic nuclei, and in the account which follows, basal ganglia will refer to all subcortical *motor* nuclei of the forebrain, *i.e.*, striatum, pallidum, exclusive of the hypothalamus, together with several brain stem nuclei such as the corpus Luysii, substantia nigra, etc. I am indebted to Dr. Margaret A. Kennard for assistance in the revision of this chapter. — J. F. F.

ANATOMICAL CONSIDERATIONS

THE basal ganglia, the most primitive part of the forebrain, occupy that region which lies between the diencephalon and the cerebral cortex (fig. 104). They are made up of three principal nuclei: (i) the globus pallidus lying medially against the internal capsule, (ii) the putamen lying just lateral to the globus pallidus, and (iii) the caudate nucleus with head and long tail lying medial to the anterior limb of the internal capsule, forming the floor and lateral wall of the lateral ventricle.* Other nuclei usually included in the basal ganglion complex are the subthalamic body of Luys, the red nucleus and the substantia nigra, although they lie anatomically in the brain stem. Histologically, the striatum is made up of large and small neurons which are differently affected by pathological agents. The pallidum, on the other hand, is made up principally of one type of cell which is obviously motor in character. Two other nuclei also included with the complex are the claustrum which lies lateral to the putamen, and the amygdala; the *claustrum* is separated from them by a white-fibred projection known as the external capsule (fig. 104). The functions and connections of the claustrum are obscure; it receives a cortical projection. The *amygdala* is a small but highly discrete nuclear mass lying on the roof of the temporal horn of the lateral ventricle, on the inferior end of the caudate nucleus. It is said to have olfactory connections, but its functions are quite unknown.

COMPARATIVE ANATOMY. Amphibians have basal ganglial nuclei, but they are relatively undeveloped and represent the archistriatum of higher forms (n. amygdalae). It receives fibres from the olfactory system, the thalamus and the hypothalamus. In reptiles basal ganglia are more extensive, have similar connections and, in addition, fibres from the paleocortex; the counterparts of the globus pallidus and of the striatum here make their appearance. In mammals the archistriatum is represented entirely by the amygdaloid nucleus, and the pallidum by the globus pallidus which is connected posteriorly with the subthalamic body of Luys and with the substantia nigra. The striatum, on the other hand, consists of the caudate nucleus and putamen, which are separated from one another by the internal capsule; the two structures are virtually identical histologically and are united by bands of grey matter. Phylogenetically there is a close parallelism between the pallidum and the development of the allocortex, while the striatum has developed *pari passu* with the isocortex.

CONNECTIONS OF BASAL GANGLIA. In considering the connections of the striatal nuclei the distinction between striatum and the pallidum is further emphasized,

* The caudate nucleus and putamen form the "striatum"; the putamen and globus pallidus are often designated the "lenticular nuclei." The three nuclear masses are collectively designated the "striopallidum."

for the newer parts of the basal ganglia are primarily intra-forebrain association centres, while the pallidum retains its ancestral function as a motor nucleus — at one time the principal motor pathway from the forebrain. The connections of the individual nuclei will be taken up separately.

Caudate nucleus. The caudate nucleus probably receives extrapyramidal projections from the frontal lobes, principally from area 4s, also from areas 6, 8 and 9 (ch. xiv), and is thought also to receive collaterals from corticospinal neurons (Cajal). It receives fibres from the thalamus (from the medial nuclei, but not from

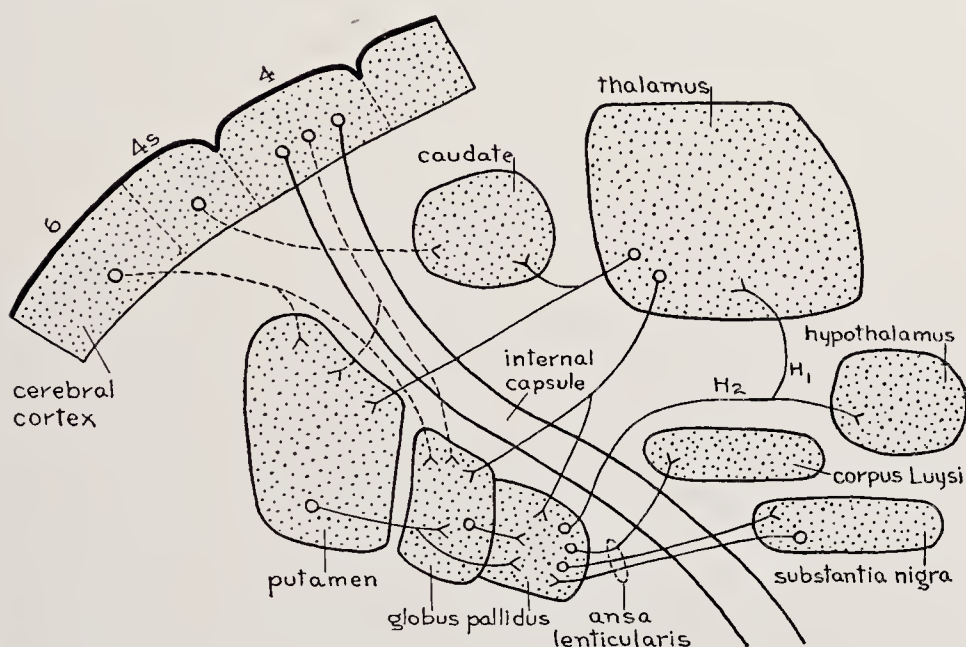


FIG. 104. Diagram of interconnections between basal ganglia and cerebral cortex. Projections from areas 4, 4s and 6 have been established by physiological techniques of Dusser de Barenne and his colleagues and are incicated by dotted lines. Note that area 4s projects only to caudate, whereas areas 4 and 6 have connection with putamen and globus pallidus (from Kennard, unpublished).

the anterior nuclei). The caudate nucleus sends fibres into the putamen and globus pallidus, but it has no direct anatomical connection with brain stem nuclei or the spinal cord.

Putamen. The putamen receives projections from area 4 and also from extrapyramidal areas of the cortex; according to Cajal, the corticospinal neurons also give off collaterals to it. It has some direct fibres from the thalamus (Walker, 1938), and has a large connection with the caudate nucleus. The putamen discharges directly into the globus pallidus (fig. 104).

Globus pallidus. The globus pallidus has extensive diencephalic connections, but its principal innervation is from the putamen and caudate; according to Polyak (1932) it also receives fibres from the cerebral cortex. The efferent pathways pass to the thalamus, particularly the centromedian and to other subcortical nuclei. Its motor projection is referred to as the *ansa lenticularis*. The principal

connections of the basal ganglia are shown in the accompanying diagram (fig. 104; see also Ranson and Ranson, 1939; 1942).

Studies of the descending pathways from the globus pallidus indicate 16 discrete brain stem centres, but no fibres that pass to the spinal cord (Morgan, 1927). These nuclei are as follows: "(1) the mammillo-infundibular nucleus of Malone; (2) substantia reticularis hypothalami of Malone (cephalic part), (nucleus of Forel's field) of the same and opposite sides; (3) the subthalamic nucleus of Luys; (4) the subthalamus ventrocaudal to the thalamus (caudal part of the substantia reticularis hypothalami); (5) interstitial nucleus of Cajal and nucleus of Darkschewitsch; (6) oculomotor nucleus and nucleus of Westphal-Edinger; (7) red nucleus (?); (8) motor division of the substantia nigra (intrapuduncular nucleus of Malone); (9) peripeduncular nucleus of Jacobsohn. Through a striobulbar fasciculus, fibres terminate in: (10) the trochlear and abducens nuclei; (11) reticular nuclei of the pons and medulla (not definitely proved); (12) masticator nuclei; (13) facial nuclei; (14) ambiguous nuclei; (15) hypoglossal nuclei; (16) through Meynert's commissure to the globus pallidus and region of Forel's field H₂ of the opposite side."

The ansa lenticularis forms the principal extrapyramidal projection from the old part of the forebrain (Papez, 1942). The striate systems are sometimes grouped together under the term "extrapyramidal system" and lesions of the striate bodies and pallidum are usually referred to as producing "extrapyramidal syndromes." This terminology is unfortunate since it has carried with it the erroneous implication that it is the only extrapyramidal motor system of the forebrain. The extrapyramidal projections from the cerebral cortex have already been described in detail and, since their destinations in red nucleus, substantia nigra, etc., are similar to that of the ansa lenticularis, it is no longer justifiable to think of the extrapyramidal system as a purely subcortical mechanism. By means of connections with the red nucleus whose spinal projection crosses in the decussation of Forel, the basal ganglia establish a primarily contralateral control over the bodily musculature, although part of the projection from the striate bodies goes to the opposite red nucleus, making possible here also, by virtue of double decussation, some degree of ipsilateral control over the body musculature.

Subthalamic nucleus of Luys Although not strictly a part of the basal ganglia complex, the subthalamic nucleus of Luys is functionally bound up with the globus pallidus and for this and other reasons merits description in a discussion of the basal ganglia. The boundaries of this nuclear mass are sharp in man, less clear in the macaque and lower primates, and indistinct in other mammals. Relatively, it is much larger in man than in any animal, which indicates the importance of a comparative analysis of its functions. It is made up of medium sized spindle-shaped cells with unequally distributed chromatin. For many years it has been known that its primary afferent connection is with the globus pallidus. Its efferent connections have been worked out in detail on dogs as follows: (i) in a comma-shaped nucleus, lying medial to the substantia nigra; (ii) in the ventral and medial capsule of the red nucleus; (iii) a few crossed fibres end on the same structures on the opposite side of the brain stem.

Substantia nigra. Lying in the midbrain between the *basis pedunculi* and the tegmentum is a greyish-black region of nuclear material forming a crescent which Soemmering (1800) designated the "substantia nigra." In cross-section, the substantia nigra is found to extend throughout the length of the mesencephalon in lateroventral relation to the red nucleus. It is pierced by fibres from the various eye muscle nuclei. The substantia nigra receives fibres from the more rostral divisions of the extrapyramidal system, particularly from areas 4 and 6 of the cortex

and from the globus pallidus via the ansa lenticularis. It appears to send fibres to the red nucleus and probably to the medulla, but not to the spinal cord (see Finley, 1936).

Red nucleus. The red nucleus is lodged in the mesencephalon just superior to the substantia nigra (ch. xi). It is made up of two distinct cellular groups, a phylogenetically older division made up of large cells and lying toward the caudal end of the nucleus, which gives rise to the rubrospinal pathways; and a second and larger division which includes the rostral two-thirds of the nucleus and receives fibres from the dentate nucleus of the cerebellum as well as from the thalamus, globus pallidus and frontal lobes. The former large-celled division of the red nucleus has become relatively small in man; the latter and larger division gives rise to two large fibre systems: (i) that to the lateroventral nucleus of the thalamus (ch. xiv), which in turn projects to areas 4 and 6 of the cortex, and (ii) a descending fibre system to the reticular formation. The functions of the red nucleus are intimately bound up with those of the reticular formation.

EXPERIMENTAL STUDIES

No field of neurophysiology has progressed more rapidly in the past five years (1938-43) than has the analysis of the basal ganglia and their interrelation with the cerebral cortex; as Bucy (1942) has remarked, "the facts are now falling together like well fitting pieces of an intricate jigsaw puzzle." The story *is* in some ways intricate, but relationships are now clear which six years ago were almost complete chaos. The principal facts can be summarized under the headings of: (i) stimulation, (ii) lesions and (iii) the cortico-striato-pallido-thalamo-cortical circuits.

STIMULATION. Kinnier Wilson (1914), using the Horsley-Clarke technique, stimulated the putamen and globus pallidus of monkeys with an intensity of stimulus greater than that adequate for the motor cortex and found both nuclei completely inexcitable. Occasionally, when moving the stimulating needle through the substance of the striate nucleus or the pallidum slight movements occurred, "but these were always variable, inconstant and fleeting. First of all, it was sometimes found that homolateral movements of the face, mouth, or tongue took place with stimulation toward the outer surface of the putamen and external capsule. These were neither strong nor persistent." Other reports of striatal stimulation mentioned in the first edition of this book are open to question of the spread of stimulating currents. Miller (1936) observed slow movements of the legs of cats following stimulation of the caudate nucleus under Dial anesthesia. Rioch and Brenner (1938) recorded a variety of response from the basal ganglia of dogs and cats whose cerebral hemispheres had been removed three weeks previously;

the chop-licking, salivation, swallowing, sniffing, etc., which they mentioned(see above ch. xvi)were the principal motor responses, and these can be attributed to the olfactory system rather than to the striopallidum. *In none of the animals were there phasic movements of the extremity, body or tail, unless an extremity happened to be maintaining a posture, in which latter case stimulation of the caudate nucleus caused a prompt inhibition of the posture.*

Inhibition from the striatum. Tower(1936)first emphasized that basal gangliar reactions must be examined against a background of posture or movement; in attempting to follow the subcortical pathways of the extrapyramidal inhibition obtainable from the cerebral cortex after section of the medullary pyramids, she found that the striopallidum gave much more vigorous inhibitory responses than the adjacent internal capsule. Rioch and Brenner's studies just alluded to are in keeping with this disclosure, and a more recent analysis of Mettler, Ades, Lippmann and Culler(1939)gives further experimental support of a substantial character. Stereotaxic electrodes were applied to the basal ganglia of cats and monkeys during concurrent contraction evoked by stimulation of the motor cortex. No primary motor responses could be obtained from the caudate, but cortically evoked movements were dramatically inhibited from this nucleus. The threshold was lower than that required for excitation of the fibres of the internal capsule; the inhibitory reaction was unobtainable if the caudate had previously been fulgerated. The response was wholly confined to ipsilaterally evoked movements, and the inhibition often persisted for several minutes after withdrawal of the inhibitory stimulus(as with the area 4s suppressions of Dusser de Barrenne and McCulloch). From the putamen and claustrum similar effects were obtained but to a lesser degree. The authors state that the globus pallidus, which also gave no motor responses, caused a conversion of the cortically initiated movements into "plastic tonus."

LESIONS. Studies of the sequelae of circumscribed striate lesions have been on the whole disappointing, but they clearly illustrate that the striatum has taken a conspicuous part in the process of functional encephalization, and that the syndromes of injury in lower animals are only remotely applicable to man. Thus in cat and dog, and even in monkey, large lesions of the basal ganglia cause little basic disturbance of motor function. In the chimpanzee, however, Kennard(1943; Kennard and Fulton, 1942; Brown, 1939)has clearly demonstrated, following striatal

injury, athetoid movements closely comparable to those seen in the human being.

Kinnier Wilson(1914) found that small lesions restricted to any part of the striate complex caused no sign of motor impairment. With larger lesions, especially when bilateral, there followed relative "absence of involuntary movement. Some of these monkeys, however, showed a preference, in the taking of nuts or bananas, for the homolateral limb, or on climbing about their cage they showed awkwardness or clumsiness of the contralateral limb. Yet no approximation to paralysis or even paresis was seen." This general conclusion has been substantiated by many subsequent investigators on cats, dogs and monkeys(Mettler and Mettler, 1942; Kennard, 1943).

Lesions involving the globus pallidus, in addition to the striatum, such as those recorded by Morgan(1927) may give rise to moderate hypertonia of the contralateral extremity, moderate restlessness is said also to supervene and there may be disturbances of the voice and mastication. In a group of 26 cats closely studied by Liddell and Phillips(1940), the majority of which had unilateral lesions involving pallidum and putamen, the principal physical sign was a slight, but persistent, hypertonia of the contralateral extensors, demonstrable when the animal was at rest with limbs hanging freely. Other sequelae were:(i) delayed flexor reflex,(ii) defective placing reactions(due probably to encroachment on internal capsule),(iii) flexor hypertonia on the ipsilateral side and(iv) defective closure of contralateral eyelid. Deafferentation was followed by temporary reduction of extensor hypertonia. Similar observations come from Mettler and Mettler(1942) but they insist that such animals also show some degree of spontaneous *hypermotility*; since they give no details concerning their mode of appraising hypermotility, and since a maximum degree of spontaneous motor activity(measured in an activity cage) follows bilateral ablation of area 13 which in no way involves the striatum(unless area 13 projects to the caudate), decision concerning the extent and significance of hyperactivity from striatal lesions must await further and better documented study. This applies also to the report of Richter and Hines(1938) for isolated injury of one, or of both caudate nuclei, if unassociated with damage to the frontal areas, fails to evoke hyperactivity in macaques(Kennard, unpublished).

Removal of the striatum from chronically decorticate cats and guinea pigs does not add further motor deficit, *i.e.*, "the posture, locomotion, rigidity, hopping and placing reactions in these animals before and three to five hours after destruction of the ipsilateral striatus failed to reveal any fresh symptoms"(Rioch and Brenner, 1938).

CORTICO-STRIATO-PALLIDO-THALAMIC INTERRELATIONS. There has been a growing conviction during the past ten years that the cerebral cortex and basal ganglia in primates are so closely interrelated functionally that they tend to act as a unit. Unlike other levels of central nervous function, such as the spinal, medullary and hypothalamic which are clearly distinguishable, there is little to differentiate a decorticate primate from a thalamic or hypothalamic preparation. This suggests that once the cerebral cortex has been removed, the basal ganglia cease to con-

tribute significantly to functional integration(Rioch and Brenner). Although this is probably not strictly true(basal ganglia preparations survive more readily than do hypothalamic)the motor status of the two preparations in adult animals appears closely similar, even though the basal ganglia do not degenerate after decortication.

With isolated lesions of cerebral cortex and basal ganglia of primates, however, Kennard has shown that precentral ablations(areas 4 and 6) when combined with striatal lesions, especially in young animals, give a more profound and enduring paralysis than the cortical lesion alone. In young animals there is a considerable degree of independent motor integration at the striatal level; as the animal matures, motor patterns of integration tend more and more to be dominated by the cerebral mantle (Kennard and Fulton, 1942).

Corticostriatal interaction. Hines(1937)observed that electrical stimulation of a small band lying between areas 4 and 6 caused cessation of spontaneous muscular activity on the opposite side and relaxation of any existing postural contraction. Upon strychninization of this same region Dusser de Barenne and McCulloch(1938a)evoked conspicuous electrical activity in the caudate nucleus. They noticed further that, with activation of the caudate, spontaneous electrical activity in area 4 was suppressed and the threshold for excitation of this area was greatly increased. The suppressor action on area 4 was not mediated transcortically, but by a complex circuit starting from area 4s through the caudate, thence (probably via globus pallidus) to the latero-ventral relay nuclei of the thalamus and back to area 4. Strychninization of areas 4 and 6 themselves had no such effect on the caudate; isolation of the caudate caused disappearance of strychnine suppression from area 4s(Dusser de Barenne and McCulloch, 1941b). As already indicated in chapter XXI, three other suppressor areas have since been isolated(figs. 102 and 105), two of which cause specific activation of the caudate; area 8s stimulating the head of the caudate, 4s the medial part, 2s the tail, thus converging in a spatially orientated manner suggesting a well organized topographical projection. Area 19s has not been fully studied. Area 4 itself projects to the putamen and area 6 to putamen and pallidum and neither affect the caudate(Dusser de Barenne, Garol and McCulloch, 1942).

Anatomical proof of a direct projection from area 4s to caudate is still lacking. Verhaart and Kennard(1940)followed degeneration after thermocoagulation of 4s and while there was fine fibred Marchi degeneration approaching the caudate,

they were unable to prove that the fibres ended there. Levin(1936)and Polyak (1932) offered similar evidence following larger lesions from the precentral area of macaques. Hirasawa and Kato(1935), on the other hand(see also Hirasawa and Kariya, 1936), believed that they traced definite projections into the caudate (ch. xv).

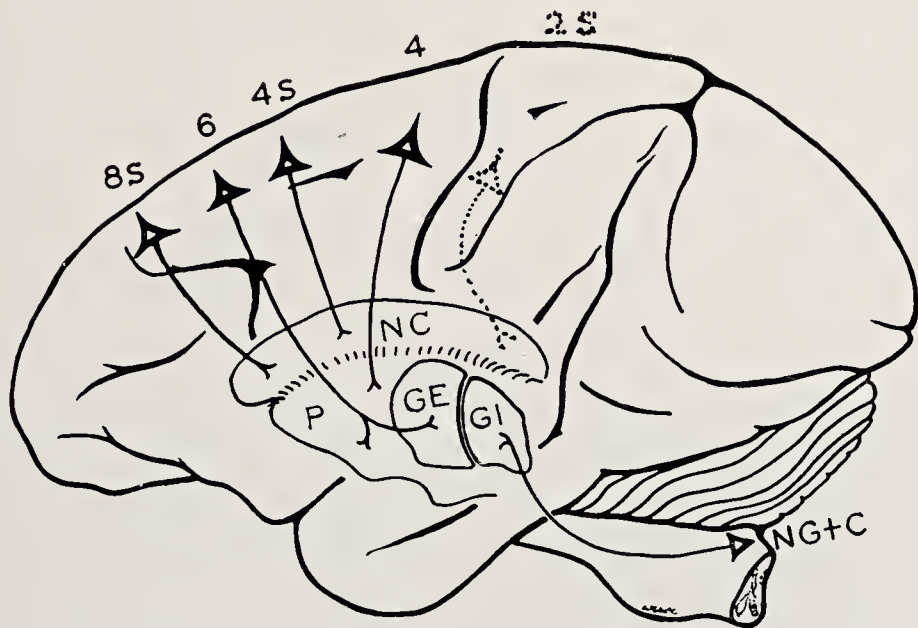


FIG. 105. Diagram showing topographical projection of suppressor areas upon caudate nucleus; area 8s passing to head of caudate, 4s to midcaudate, and 2s to tail of caudate. Area 4 projects to putamen and area 6 to putamen and external division of globus pallidus. Globus pallidus in turn projects to relay nucleus of thalamus, and thence the thalamic nuclei project back to areas 4 and 6 as indicated in figure 106.(From Dusser de Barenne, Garol and McCulloch, 1942).

If this elaborate circuit from area 4s to caudate to pallidum, to thalamus and back to area 4 is interrupted at any point subcortically, the restraining effect exerted by the basal ganglia would then be withdrawn, and Bucy(1942) has given a convincing interpretation of the more common basal gangliar syndromes based on these newer physiological disclosures (see next section).

Electrical potentials of basal ganglia. Electroencephalographic investigation of animals having lesions of subcortical nuclear masses has recently given additional evidence of the interdependence of cortico-striatal functions. Although, in monkeys, ablation of large parts of the cortical gray matter has no effect on the EEG, lesions of the basal ganglia permanently alter the resulting pattern of electrical potentials (Kennard and Nims, 1942b). Furthermore, it has been shown that the

pattern of the EEG obtained from the exposed caudate or putamen is materially affected when in connection with cortical areas, *i.e.*, the basal ganglia of a partially decorticate monkey yield an altogether different pattern from that of a totally decorticate preparation. Spontaneous bursts of high-voltage activity appear from caudate and putamen only when all connection with the cortex has been severed (Kennard, 1943a).

Similar evidence of the interdependence of the *thalamic nuclei* with the postcentral cortex has been obtained by Morison and Dempsey (1943). They have analyzed the induced and spontaneous patterns of electrical activity from the cortex during stimulation at various levels of afferent projection to the sensory cortex. Characteristic patterns which are consistently altered by thalamic lesions have been thus obtained.

CLINICAL PHYSIOLOGY

The clinical syndromes of the basal ganglia, which for so long have mystified neurologists and physiologists, are fully described in standard neurological texts such as that of Kinnier Wilson (1936), Grinker (1943), Wechsler (1943), etc. The syndromes that lend themselves to physiological interpretation are those of athetosis, tremor of paralysis agitans, and the intention tremors of cerebellar diseases (to be discussed in the next chapter).

ATHETOSIS. Athetosis refers to the involuntary movements of the skeletal musculature, slow and writhing in character, generally involving the upper extremities more extensively than the lower and the distal joints more severely than the proximal. Sometimes quick and jerky movements complicate the slower sinuous variety, and in these circumstances, the term choreo-athetosis is applied. The syndrome is prone to develop during the first two decades of life, but it may occur later, and it is now recognized that the most common pathological lesion associated with athetosis and choreo-athetosis is an affection of the striate nuclei, so-called *status marmoratus*, from the fact that on microscopic section the striate nuclei appear like marble. The intimate nature of the pathological lesion is unknown, some attributing the primary affection to a change in the myelin of the axis cylinders; others, to a toxic reaction among the cells of origin in the striatum. Although the predominant lesion is the striatum (Alexander, 1942), Schuster (1927) in an extensive study of thalamic lesions has demonstrated that isolated destruction of the ventrolateral nucleus of the thalamus may also be as

sociated with athetosis, especially if it involved the striato-thalamic connections. Papez, Hertzman and Rundles(1938) have similarly described a case of athetosis in which the lesion was sharply localized bilaterally in the globus pallidus. *Thus all three of the stations which cause athetosis lie in the circuit of the suppressor reactions between areas 4s and 4.*

In 1909 Horsley upon removal of the precentral cortex in man was able to cause abolition of involuntary movements of athetosis. Similarly, Bucy and Buchanan(1932) reported a number of dramatic cases of abolition of athetosis following lesions restricted to area 6. The belief that choreiform and athetoid movements stem ultimately from the cerebral cortex was originally propounded by Kinnier Wilson, who pointed out that these abnormal movements, as with the cerebellar ataxias, represented an attempt on the part of the cerebral cortex to compensate for faulty subcortical mechanisms. Bucy(1942) argues that the movements are due to motor projections other than those of the pyramidal tract, since under barbiturate anesthesia abnormal movements disappear, while isolated pyramidal movements are still possible. It is known that the barbiturates abolish the excitability of area 6, leaving that of area 4 and pyramidal tract relatively unaffected. He proposed further that these non-pyramidal projections of areas 4 and 6(which he designated the *parapyramidal pathways*) being released from suppressor action, are directly responsible for the athetoid movements(fig. 106).

Bucy(1942) mentions that Putnam(1933) brought most welcome support to this hypothesis by demonstrating that sectioning of the anterior columns of the spinal cord, sparing the lateral pyramidal tract, would materially reduce or abolish involuntary athetoid movements. Both Putnam and Bucy have expressed the belief that in sectioning the anterior columns of the spinal cord one is probably interrupting part of the same parapyramidal system destroyed by Bucy in removing the precentral cortex. It is obvious, however, that primary neurons are attacked in the cerebral cortex, while the spinal cord operation severs neurons lower in the chain and arising from a subcortical center. From this Bucy draws the following conclusions:(i)involuntary movements of athetosis develop as a result of nerve impulses from suprasegmental centers conveyed along neurons other than those of the pyramidal tract;(ii)that these impulses are transmitted from the cerebral cortex by way of the parapyramidal fibers arising in areas 4 and 6;(iii)that these fibers terminate in various subcortical centers and pass their influence to the spinal cord via secondary neurons;(iv)that in the spinal cord the fibers concerned lie for the most part in the anterior columns.

All this is in keeping with the fact that when a hemiplegia develops in a patient having athetosis involuntary movements disappear in the paralyzed extremities. From these considerations it follows that in cases

of extreme athetosis relief may be expected either from ablation of area 6 of the cerebral cortex or from chordotomy of the anterior columns of the spinal cord. To date the most enduring and satisfactory results have been those following the cortical operation.

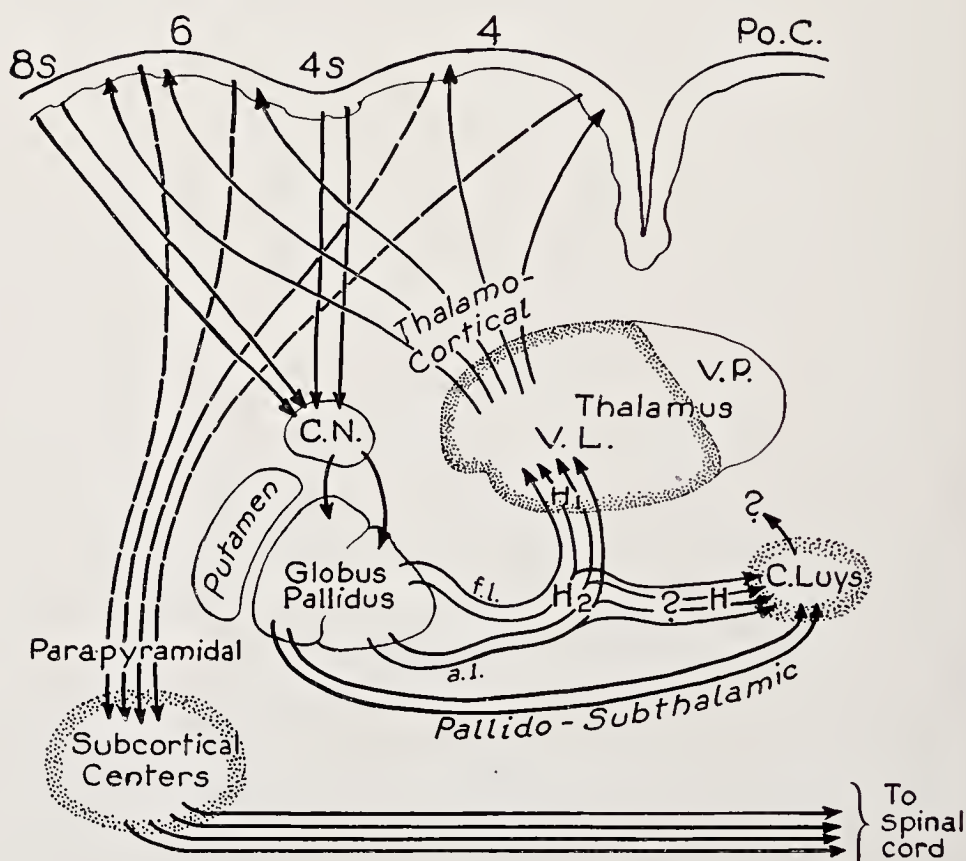


FIG. 106. Neural mechanism of choreo-athetosis. Inhibitory impulses arise from the suppressor strips 8s and 4s and pass to caudate nucleus (C.N.); they pass from there to globus pallidus; thence from internal division of *globus pallidus* (Ranson and Ranson) through *fasciculus lenticularis* (f.l.) and *ansa lenticularis* (a.l.) into field H₂ and through field H₁ into the antero-lateral part of the ventro-lateral nucleus of the thalamus (V.L.) (Papez); from there thalamo-cortical fibres return suppressor impulses to precentral cortex, more to area 6 than to area 4 (Papez). If this suppressor mechanism is interrupted in *striatum* (Alexander) or *globus pallidus* (Papez) or thalamus (Schuster) the *parapyramidal* system arising from areas 4 and 6 will be released to abnormal activity resulting in involuntary movements of choreo-athetosis. This diagram also illustrates possible pathways for similar suppressor fibres from 8s and 4s to the caudate nucleus and globus pallidus and thence to the subthalamic nucleus of Luys (C. Luys) either by way of the fasciculus and ansa lenticularis, and fields H₂ and H₁ (Papez) or by way of pallido-subthalamic bundle from external division of globus pallidus as described by Ranson and Ranson. How these suppressor impulses return to precentral cortex is unknown but their interruption in corpus Luysi results in hemiballismus (Bucy, 1942).

TREMOR OF PARALYSIS AGITANS(PARKINSON'S DISEASE). Advanced cases of Parkinsonism generally exhibit rigidity and a postural tremor, usually designated a tremor of rest. The so-called tremor of rest disappears during sleep, is exaggerated by emotion, and is generally seen in those muscles in which a posture is being maintained by a semi-voluntary effort. Those who have studied Parkinson tremors in detail insist therefore that it is not strictly speaking a tremor of rest, but a tremor of action concerned with stance or posture, as contrasted with the phasic intention tremor seen in cerebellar disease. All tremors, therefore, are tremors of action, paralysis agitans being one of active posture, cerebellar disease being one of active movement. The mechanism involved in Parkinson tremor is not clearly established, but the substantia nigra and globus pallidus have been the structures most commonly indicted(Alexander, 1942). In view of the known connection between the substantia nigra and globus pallidus it is clear that a lesion in either nigra or pallidus might implicate the same neural mechanism. The existence of cortico-nigral fibres from the premotor area(Levin, 1936)suggest a circuitous mechanism similar to that involved in athetosis.

Bucy(1942)points out that a capsular hemiplegia abolished Parkinson tremor; with this in mind Bucy and Case(1937)removed the precentral cortex in an advanced case of Parkinsonism; the operation was followed by a virtually complete and enduring abolition of tremor. Similar results have been reported by Klemme(1942), Putnam(1940)and Oldberg (1938)demonstrated that anterior quadrant chordotomy has no influence upon this type of tremor, and that the evidence points to the pyramidal tract, as opposed to the parapyramidal system, as being implicated in the production of these involuntary movements. Bucy's successful cases involve both areas 4 and 6, and it now seems probable that an operation restricted to area 4 alone is the operation of choice for advanced Parkinson tremor.

Rigidity. Associated with Parkinson tremor is generally some degree of muscular rigidity. In cases of Parkinsonism, however, the rigidity may develop before the tremor, or vice versa, and the two can clearly exist as separate entities, suggesting that different mechanisms are involved in their production. The rigidity is quite different in quality from the spasticity produced by lesions of the agranular frontal cortex: it involves both flexor and extensor muscles, it lacks the clasp-knife quality seen in decerebrate rigidity, and is said to be uninfluenced by the labyrinthine reflexes, but it may be exceedingly intense. Tendon reflexes may be normal or exaggerated and there is no clonus. When passively moved, a characteristic intermittent("cog-wheel")resistance may be felt throughout the extent of

the passive movement. The rigidity is probably ultimately myotatic in origin since it depends upon the integrity of the posterior roots and proprioceptive nerve endings in muscles (Foerster, 1921; Byrnes, 1926; Walshe, 1924). It develops in unmistakable form in chimpanzees following basal ganglion lesions, especially when combined with lesions of area 6 (Kennard, 1943c).

The neurological basis of the symptom complex is not clear, for the globus pallidus, substantia nigra, and subthalamic body of Luys are all likely to be involved in cases of Parkinsonism, changes in the substantia nigra being the most constant and sometimes the principal pathological finding (Alexander, 1942). These three structures are closely linked phylogenetically and anatomically, and recent pathological studies indicate that the globus pallidus and substantia nigra are seldom independently involved; if one is affected, the other is likely to be implicated as well, but in early cases the lesion of the substantia nigra appears to be primary. The extent of involvement of the subthalamic body of Luys varies.

Hemiballismus. Isolated lesions of the body of Luys in man also give rise to coarse choreiform movements, especially of the upper extremities; the arm may be hurled precipitately outward or upward, quite uncontrollably. These purposeless movements are generally referred to as "*hemiballismus*." Bucy (1942) has presented an interpretation of hemiballismus as a release from suppressor mechanisms similar to that described above for choreo-athetosis (fig. 106).

Associated movements. Associated movements are automatic modifications of the attitude of certain parts of the body when strong volitional or reflex movements occur in some other part. They are most commonly observed in the paralyzed upper limb of a hemiplegic patient when he executes a grasping movement with the sound hand; in these circumstances, an "associated" increase of tone occurs in the muscles of the paralyzed limb, predominating in the flexor muscles. In normal persons there are also semi-voluntary associated movements, such as swinging of the arms when walking, or the extension of the wrist with normal flexion of the fingers. These latter reactions are prone to be impaired or abolished in the presence of clinical lesions of the basal ganglia. The Vogts (1920) maintained that disturbance of associated movements is a primary symptom of striatal disease. Kinnier Wilson (1925) (Lecture 2), on the contrary, has put forward the hypothesis that "striatal disease is not characterized by complete outfall of 'associated movements'; naturally, we do not expect the special variety discoverable in pyramidal affections to be present in extrapyramidal disease, and therefore cannot in any sense describe it as 'lost.'" Wilson's cautious attitude is well taken, but the fact remains that many of the more common associated reactions are "lost" or wholly obscured by rigidity in cases of advanced Parkinsonism.

DISCUSSION

As set forth in chapter XXI, the extrapyramidal motor system has two primary subdivisions: (i) the corticopontocerebellar and the (ii) corticostriatonigral. Each division has three levels of function, the superior being cortical, and at the cortical level the two primary divisions are inseparably intermingled, suggesting that the discrete function subserved by the two divisions are here correlated in common integration (Fulton, 1943).

The functions of the corticopontocerebellar division will be described in the next chapter; those of the corticostriatonigral system are summarized here. Before discussing these functions in detail, it is important to bear in mind the following facts: (i) Interruption of the *pyramidal* pathway itself causes no increase in tone of the skeletal muscles (ch. xx). (ii) Interruption of the *extrapyramidal* pathway, on the other hand, at any supramedullary level, be it cortical or subcortical, causes, through release of mesencephalic or medullary centres, conspicuous augmentation of tonus. The character of these hypertonic disturbances varies with the level of interruption as follows:

(i) *Cortical level*. As indicated in chapter xx1, interruption of the extrapyramidal projections of the cortex causes both spasticity and rigidity, the intensity and distribution of the hypertonic states varying with the extent of the interruption; at the cortical level, however, the spastic element predominates.

(ii) *Striatal level*. Interruption at the striatal level, especially when the globus pallidus is involved, appears to cause rigidity of the peculiar type described above. Whether this rigidity is independent of simultaneous interruption of cortical and nigral projections is not yet settled.

(iii) *Mesencephalic level*. Interruption at the mesencephalic level gives great intensification of rigidity (substantia nigra) and of spasticity (reticular formation). When the brachium conjunctivum is also interrupted, there develops a maximum of spastic rigidity, *i.e.*, complete release of the medullary centres from extrapyramidal control (decerebrate rigidity, ch. ix).

The corticostriatonigral system thus has, as its name implies, three distinct levels of integration: cortical, striatal and mesencephalic. The first two levels have already been considered. The mesencephalic level includes principally the substantia nigra that part of the red nucleus having connection with the globus pallidus. The subthalamic body of Luys is perhaps best grouped with the third level of extrapyramidal functions, although it lies slightly anterior to the mesencephalon (in the posterior diencephalon). Isolated lesions of the substantia nigra have not been studied in experimental animals, but in man they are associated with rigidity and disturbances of associated movements similar to those which occur in clinical extrapyramidal disease. It is obvious, therefore, that the extrapyramidal system with its three levels should be considered as a unit and it becomes necessary to inquire what general function the sys-

tem serves, and how it may be distinguished from the functions subserved by the corticopontocerebellar mechanism(ch. xxv).

Speaking generally, the corticostriatonigral system, as thus defined, is responsible for postural adjustments and the integration of *involuntary* movement patterns. Thus, with a lesion of the globus pallidus posture is disturbed and associated movements, such as the swinging of the upper extremities with walking, are abolished; movements of the face appropriate to particular emotional states are similarly lost. These automatic reactions which are beyond the sphere of conscious integration may be replaced by purposeless contortions over which the subject has no control(athetosis and chorea). Disturbances involving the cerebellar mechanism, as we shall see, are in the sphere of conscious volitional movement. Indeed, neocerebellar disturbances are seldom manifest except *during* volitional effort.

The complexity of the disturbance in the extrapyramidal sphere varies with the level of the lesion. Thus associated movements are lost following lesions of area 6 of the cortex, but more complex patterns of motor organization also vanish; and they remain permanently disturbed, whereas disturbances of reflexes and associated movements tend to disappear.

Clinical and experimental studies on the striatum are in essential harmony in one point, namely, that small isolated lesions of the striatum which clearly affect no other adjacent structures cause few, if any, recognizable symptoms. It therefore seems probable, to quote Rioch and Brenner, "that the so-called striatal symptoms are due to lesions which involve other brain areas at the same time. These considerations suggest the following hypothesis, namely, that in the mammal the striatum does not have an autonomous function, but acts only in conjunction with other systems."

SUMMARY

The basal ganglia consist of three primary nuclei: caudate, putamen and pallidum and two secondary cellular masses, the amygdala and claustrum; the subthalamic body of Luys, the red nucleus and the substantia nigra are also intimately bound up with the basal ganglion mechanism. The caudate and putamen nuclei(the striate bodies)are fore-brain association centres having connections with the frontal lobes, the

thalamus and the hypothalamus, but no efferent projections except to the globus pallidus.

The globus pallidus is the primary motor nucleus of the basal ganglia, sending, via the ansa lenticularis, fibres to all the important brain stem nuclei, including hypothalamus, subthalamic body of Luys, the oculomotor nuclei, substantia nigra, red nucleus, etc.

The subthalamic body of Luys is closely connected anatomically with the globus pallidus and discharges to a discrete comma-shaped nucleus lying just lateral to the substantia nigra.

The basal ganglia are to a limited degree electrically excitable but their primary motor effects are those of inhibition of posture and movement patterns. In chronic decorticate cats turning of eyes and head to the opposite side may be obtained from the whole striate area; from the region of the pyriform lobe chewing, salivation, sniffing and other reactions associated with feeding. In acute preparations, Miller observed similar reactions and in addition slow movements of the contralateral extremities.

Discrete destruction of various nuclei in the basal ganglion complex causes inconspicuous and transient motor symptoms in animals. With large lesions of the globus pallidus the animal tends to circle to the side of the lesion and to be unduly restless (Morgan). Kennard has produced athetoid movements in chimpanzees by combination of precentral and striate lesions.

The syndromes of the basal ganglia recognized clinically fall into 2 groups: (i) those having resting tremor generally accompanied by rigidity (Parkinsonism), and (ii) those having involuntary movements (athetosis and chorea). The syndromes involving tremor and rigidity are believed to be due to primary destruction of the globus pallidus, or its motor projection, and of the substantia nigra to which it projects. It is possible that rigidity is due in part to concomitant involvement of the subthalamic body of Luys.

The syndromes accompanied by involuntary movements (athetosis, chorea, and torsion spasm) have no settled pathology, but they appear most frequently to be associated with lesions of the striate bodies (caudate and putamen) and brain stem nuclei; however, they often show simultaneous involvement of the red nucleus, substantia nigra, subthalamic body of Luys. Isolated lesions of the body of Luys cause rigidity

and awkwardness in dogs and coarse choreiform movements(hemiballismus)in man. Bucy believes that involuntary movements result from release of the precentral cortex from the suppressor circuits of Dusser de Barenne and McCulloch.

The extrapyramidal system may be regarded as a functional entity having 3 primary levels of integration: cortical, striatal and tegmental. Its principal functions lie in the sphere of postural adjustments, associated movements, and autonomic integration, each function having representation at each of the 3 levels. Since interruption of the *pyramidal* system causes hypotonia, it may be stated categorically that all hypertonic states(spasticity and rigidity)are due to supramedullary *extrapyramidal* lesions. Many associated movements are abolished or obscured by lesions at the cortical or striatal level of the extrapyramidal system and replaced by involuntary movements.

XXV

THE CEREBELLUM

HISTORICAL NOTE

In his memorable *Cerebri anatome*, published in 1664, Thomas Willis suggested that the cerebrum presided over voluntary motions and that the cerebellum governed involuntary movements. As an argument Willis stated that when the cerebellum was manipulated in a living animal the heart stopped, and if the cerebellum was removed the animal died. Suggestive indeed was the idea that the cerebellum facilitated involuntary action, even though Willis' deduction was based upon inadequate data. There was little further advance until 1809 when Luigi Rolando published at Sassari in Sardinia an account of a series of experiments in which he had removed the cerebellum from various animals including reptiles, fish and mammals. He described disturbances of voluntary movement and pointed out that the ablation did not affect sensation or mentality. Flourens in 1824 confirmed, and considerably extended Rolando's studies, and he offered the compelling suggestion that since the staggering, tremor and slurring of speech after cerebellar injury were similar to those occurring during alcoholic intoxication, alcohol probably acts primarily upon the cerebellum. Rolando and Flourens thus laid the foundations of the knowledge of effects of cerebellar ablation. Despite much experimental work in the nineteenth century, little was added to their description of the symptoms of cerebellar deficit. The chief advances during this period lay rather in the study of anatomical connections of the cerebellum; and during the twentieth century attention has been focused principally upon its phylogeny and embryology. As is frequently the case with the higher parts of the nervous system, the more significant physiological studies in recent years have come from the clinic, and especially from the war cases of Gordon Holmes (1917). There were discrepancies between clinical signs and symptoms of cerebellar disturbances in man as contrasted with signs of deficit in animals, but the comparative approach to the problem, especially the work of Larsell and his pupils, is gradually revealing the basis for these apparent discrepancies, and it is therefore essential in approaching the cerebellum first to lay hold of comparative anatomical detail.

THE cerebellum is a vast organ of the motor system lying "downstream" in the reflex arc from the motor projection systems of the cerebral cortex. For this reason the consideration of its function has been deferred until the motor activities of the cerebrum had been dealt with. Since the functions of the cerebellum have been inferred as much from study of its comparative anatomy as from direct experimentation, a brief account will first be given of its embryology and comparative anatomy (Dow, 1942b).

ANATOMICAL CONSIDERATIONS

COMPARATIVE ANATOMY. Embryologically and phylogenetically the cerebellum arises as an outgrowth of the medulla, especially from the vestibular complex of nuclei. This outgrowth, which first appears in the primitive fish, *Petromyzon*, as two lateral protuberances fused medially and anteriorly, becomes more extensively developed in fishes and reptiles. Since the vestibular nuclei are well known to subserve postural adjustments of the labyrinthine mechanism, one would anticipate that the cerebellum might be concerned with an elaboration of vestibular functions. This actually is true, but even in primitive animals the cerebellum also has connections with other parts of the brain-stem and spinal cord. In *Petromyzon*, one of the most primitive of vertebrates (Herrick, 1924), the cerebellar anlage receives fibres from the bulb, tectum and spinal cord. Not till the amphibia are reached in phylogeny does one encounter the fundamental pattern of cerebellar morphology. In salamanders there is an anterior component receiving trigeminal and spinal fibres; it is fused in the midline and thus forms a true corpus cerebelli lying over the medulla oblongata (Larsell, 1923). The vestibular connections of salamanders, however, do not unite but protrude laterally as two distinct lobes (the "auricular" lobes) from the vestibular and lateral line nuclei. In the reptiles the two auricular lobes have become fused in the midline and as a fused entity they foreshadow the flocculonodular lobe of higher animals. Birds have a well developed and completely fused flocculonodular lobe.

The fundamental landmark of cerebellar morphology is the "fissura posterolateralis," which separates the flocculonodular lobe from the corpus cerebelli (Larsell, 1937). This fissure in lower vertebrates is found lying between the auricular lobes and the corpus cerebelli; in higher animals it is the first fold to appear in the embryological development of the cerebellum, which is in harmony with the fact that it is the earliest cerebellar fissure in phylogenetic history. In higher forms, therefore, these two primary divisions of the cerebellum require separate consideration.

Flocculonodular lobe. This lobe, a direct outgrowth of the vestibular margin of the rhombic lip of the medulla oblongata, etc., is the most constant structure in the cerebellum throughout the vertebrate series. From the studies of Larsell and Dow (1935), it is known that the flocculus and nodulus are the only parts of

the cerebellum that receive and send fibres exclusively to the vestibular nuclei (fig. 107).

Corpus cerebelli. In amphibia, reptiles and birds, the corpus cerebelli is a very simple cellular mass, forming an arch over the medulla oblongata. In the reptiles, however, a sulcus develops, the *fissura prima* of Elliot Smith, which divides the corpus cerebelli into an anterior and a posterior lobe. A secondary fold, the so-

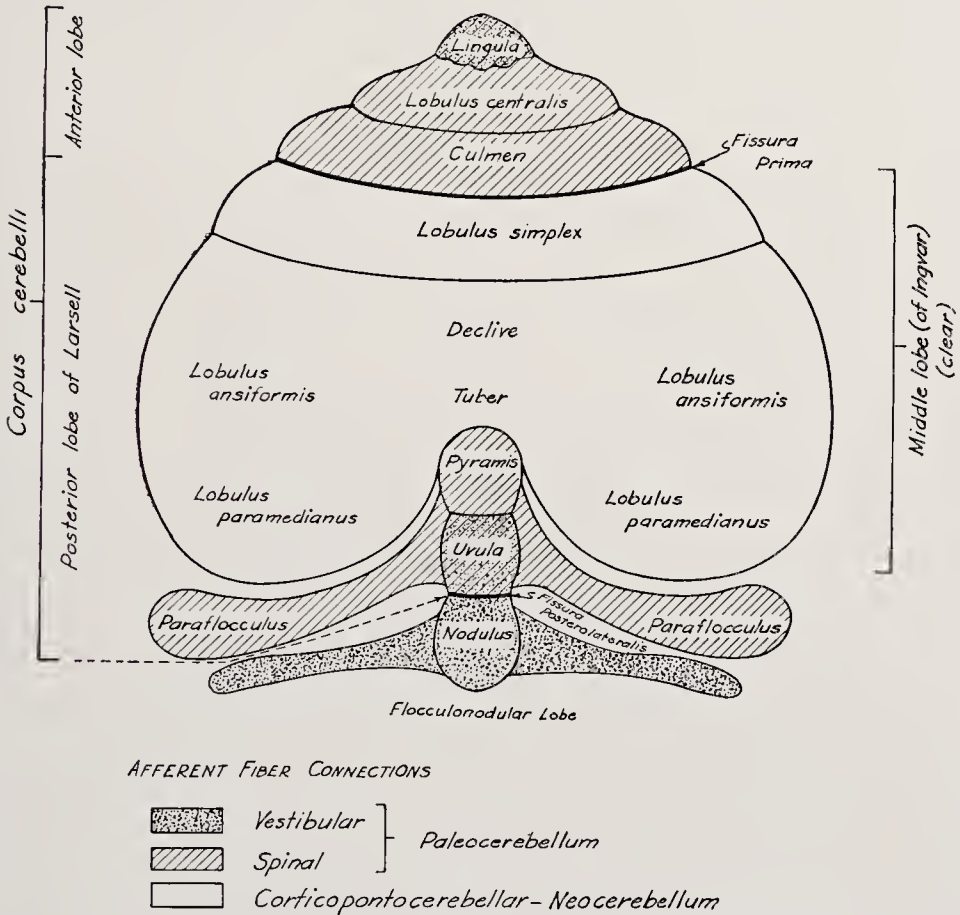


FIG. 107. Diagram of primate cerebellar cortex to show principal divisions and afferent fibre connections (after Larsell). The fissura posterolateralis separates the two primary divisions, flocculonodular lobe and corpus cerebelli (see text).

called *fissura prepyramidalis*, develops in the posterior lobe. The part of the *posterior lobe* lying between fissura prima and prepyramidalis becomes enormously developed in mammals in association with the differentiation of the skeletal musculature and the growth of the cerebral hemispheres. In the primates, this division of the cerebellum becomes so greatly elaborated that it literally overshadows all the rest of the cerebellum. Because of its recent phylogenetic history, this part of the posterior lobe is known as the *neocerebellum* and is characterized by a new connection with the brain-stem, namely, the pontocerebellar tract, from the pontine nuclei which are in direct connection with the cerebral cortex.

The *anterior lobe*, made up of lingula, centralis and culmen (figs. 107, 108), and the posterior part of the posterior lobe, made up of pyramis, uvula and para-flocculus, being phylogenetically old, are often referred to as the *paleocerebellum*. This general term may also include the flocculonodular lobe.

These phylogenetic divisions of the cerebellum have characteristic efferent connections with the rest of the brain, the details of which may be

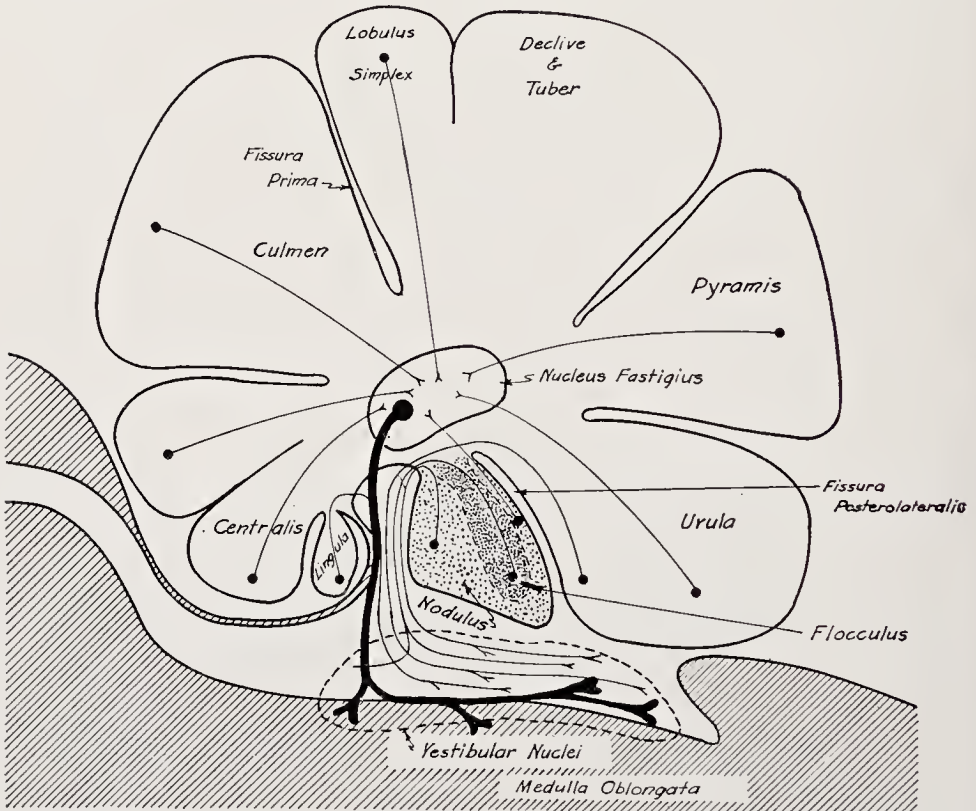


FIG. 108. Diagram to show connections from cerebellar cortex to fastigial and vestibular nuclei. Corpus cerebelli in white; flocculonodular lobe stippled.

summarized as follows (the efferent connections will be described below with the cerebellar nuclei):

AFFERENT CONNECTIONS. Larsell's division of the mammalian cerebellum is entirely substantiated by the distribution of its efferent fibres.

The cerebellum is connected with the rest of the brain-stem by three pairs of peduncles: superior (brachium conjunctivum), middle (brachium pontis) and inferior (corpus restiforme, and juxtarestiforme). The *superior* peduncles are made up chiefly of efferent fibres to the red nucleus and thalamus with a scattering of fibres to the tegmentum and bulb, but it also contains a large afferent bundle

from the ventral spinocerebellar tract of Gowers. The *middle* cerebellar peduncles are constituted almost solely of afferent fibres from the pontine nuclei; a few fibres to and from the reticular formation also pass through the middle peduncle. The *inferior* peduncles have complex connections, chiefly afferent, including the dorsal spinocerebellar tract of Flechsig, fibres from the gracile and cuneate nuclei (dorsal and ventral arcuate fibres), oliveocerebellar fibres (and cerebello-olivary), vestibulocerebellar fibres, vestibular root fibres, as well as connections from the trigeminal, and possibly from glossopharyngeal and vagus nuclei. With these also are *efferent* connections, *i.e.*, the hook bundle, or uncinat fasciculus of Russell, and a large projection from the nodulus and fastigial nuclei to the vestibular nuclei (Dow, 1942b).

Anterior lobe. The principal afferent connection of the anterior lobe comes from the spinocerebellar tract of Gowers, which is distributed to the lingula, centralis and culmen, and some fibres apparently go to lobulus simplex. The lateral limits of distribution of these fibres are not entirely clear and there is undoubtedly some overlapping between the areas of spinocerebellar projection and the projections from the pontine nuclei. The lingula also receives a few fibres from the vestibular nuclei via the inferior peduncle. The anterior lobe probably receives fibres from the trigeminal nucleus.

Neocerebellum. The part of the posterior lobe lying between fissura prima and fissura prepyramidalis, including the ansiform and paramedian lobes as well as declive and tuber in the midline, all receive afferent projections from the pontine nuclei. The neocerebellum receives few spinocerebellar projections except in some transitional regions such as lobulus simplex. The pontine projection terminates only in the neocerebellum (Dow, 1942b, fig. 109).

Pyramis, uvula and paraflocculus. The paleocerebellar part of the posterior lobe receives a spinocerebellar projection, also projections from the brain-stem, and probably from cranial nerve nuclei, *i.e.*, trigeminal. The uvula has a scattering of vestibulospinal fibres (fig. 109).

Flocculonodular lobe. The flocculonodular lobe receives fibres directly from the eighth nerve. The work of Dow (1942) indicates that in rats, cats and monkeys secondary vestibular fibres pass also to the flocculonodular lobe and are bilaterally distributed. As already mentioned, a few vestibular fibres pass also to the uvula and lingula.

The anatomical subdivisions and principal afferent connections of the cerebellum may then be *summarized* in accordance with Larsell's scheme (figs. 107-109) as follows: The cerebellum of man, and indeed of all vertebrates, has two primary divisions: (1) the *flocculonodular lobe*, the most ancient part of the cerebellum, with primarily vestibular connections. It is separated from the rest of the organ by the fissura posterolateralis of Larsell; (2) the *corpus cerebelli* which constitutes the bulk of the cerebellum is composed of two general divisions in accordance with its afferent nerve supply; (i) a paleocerebellar portion receiving vestibular and spinocerebellar fibres is made up of the anterior lobe (lingula, centralis and culmen), and a posterior part, also midline, consisting of pyramis, uvula and paraflocculi; (ii) a neocerebellar division

constituting the greater part of the corpus cerebelli, whose afferent connections are principally corticopontine (fig. 109; for recent reviews see Larsell, 1937; and Dow, 1942b).

Before taking up the problem of cerebellar function, some account must be given of the cerebellar nuclei and their efferent projections.

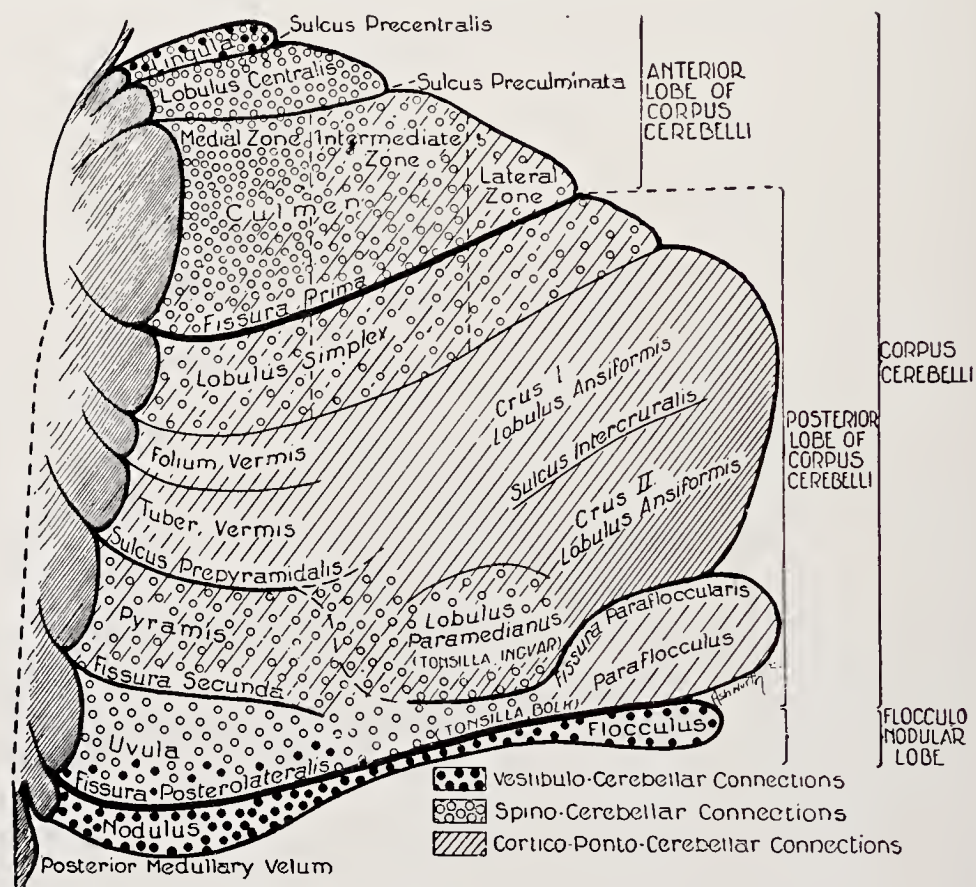


FIG. 109. Schema of the cerebellum. The brackets on the right show the divisions according to Larsell's classification. Afferent fibre connections as determined by oscillographic studies are indicated by the different types of shading (Dow, 1942b).

CEREBELLAR NUCLEI AND EFFERENT PROJECTIONS. In the more primitive mammals a simple nuclear mass appears in the middle of the cerebellum, forming the roof of the fourth ventricle; this medial nucleus is generally accompanied, even in primitive forms, by lateral nuclear masses which, below the mammals, are relatively undifferentiated. In the higher mammals, especially in the primates, the lateral nuclei become ex-

tensively differentiated generally into three groups from within outward being known as globose, emboliform and dentate nuclei. This subdivision is also recognized in the cat, and according to Brunner(1919) three lateral nuclei can be distinguished in all the primates above the lemuroidea.* The anatomical characteristics and principal connections of the cerebellar nuclei of the higher primate and man require brief description.

N. fastigii(tecti or roof nuclei). The fastigial nuclei, the oldest cellular masses in the cerebellum, occupy the roof of the fourth ventricle, extending from the base of the lingula caudally to the ventral surface of the pyramis. It is made up of large and small cells, the latter being more recent phylogenetically. The fastigial nuclei receive fibres from the entire paleocerebellum, *i.e.*, from the anterior lobe, pyramis, uvula and a few fibres from the nodulus(Dow). Via the inferior cerebellar peduncle, it also receives fibres from the vestibula nuclei and the eighth nerve. The fastigial nuclei give rise to several important efferent projections, generally referred to as the fastigiobulbar tract which includes the fasciculus uncinatus of Russell(hook bundle), which loops around the superior peduncle and then passes by the inferior peduncle to end primarily in the opposite reticular formation. Another group of fibres from the fastigial nuclei, sometimes included in Russell's bundle, pass to the opposite vestibular nuclei, but it has not yet been determined what proportion of this cerebellovestibular connection come from the fastigial nuclei and what from the flocculonodular lobe.

N. globosus(*N. lateralis anterior*), a cellular mass, lies just lateral to the fastigial nuclei and has a cellular constitution similar to that of the roof nuclei. Like the roof nuclei, it receives projections from the entire paleocerebellum, especially from the anterior lobe. It receives few if any fibres from the neocerebellum, unless possibly from the culmen. Except for a possible contribution to Russell's uncinate fasciculus, the projections of the globose nuclei pass from the cerebellum entirely by the superior peduncle to the large-celled portion of the red nucleus.

N. emboliformis(*N. lateralis posterior*) is a nuclear mass larger than globose and lies immediately lateral to it at the level of the superior peduncle. Its cells are larger than those of the dentate and are arranged in groups. The emboliform nuclei receive fibres from the paleocerebellum and also from the neocerebellum, but not from the flocculonodular lobe. Thus in its afferent connections the emboliform nuclei occupy a position intermediate between the neo- and paleocerebellum. It projects apparently entirely to the large-celled part of the red nucleus.

N. dentatus. This, the most lateral nuclear mass of the cerebellum, virtually surrounds the other nuclei in the form of two serrated half-moons. Its afferent connections are principally with the Purkinje cells of the neocerebellum, but it receives fibres from the paraflocculus and the anterior half of the dentate in its dorsomedial portion receives projections also from the anterior lobe, and the cells in this portion strain like those in the medial group of nuclei; whereas the rest of the dentate is made up of large multipolar cells with richly branching dendrites (Dow, 1942b). The dentate nucleus projects via the superior cerebellar peduncle to the small-celled part of the red nucleus. According to Mussen(1927-29), a few

* Dow(1942b)doubts whether the emboliform and globose nuclei can really be distinguished below the anthropoids. Even in macaques he designates the entire emboliform-globose complex, "nucleus interpositus."

fibres also go to the large-celled part and Walker(1938)describes fibres passing also to the pretectal region of monkeys and chimpanzees. The more important projection of the dentate nuclei in man, however, is that to the latero-ventral nucleus of the thalamus by which it establishes connection with areas 4 and 6 of the cerebral cortex. *The dentate nucleus thus contributes little direct influence to the rubrospinal pathways since these arise from the large-celled part of the red nucleus;* its primary connections are with the cerebral cortex.

Flocculonodular lobe. Although not a cerebellar nucleus in the strict sense, the flocculonodular lobe deserves consideration here since, as Dow has shown(1936, 1938c), it receives and sends fibres directly to the vestibular nuclei. Indeed, the principal part of the cerebellovestibular connection appears to come from the nodulus rather than from the fastigial nuclei. The lingula also sends a few direct vestibular fibres(Hohman, 1929).

The cerebellar nuclei has been variously classified from the point of view of their phylogenetic history. The fastigial and globose are clearly paleocerebellar. The emboliform is intermediate because it receives some projections from the neocerebellum, but the dorsomedial frontal portion of the dentate is also intermediate since it receives paleocerebellar projections. This has led Brun(1925)to classify the caudal half and the ventrolateral part of the frontal half of the dentate nucleus as neocerebellar, and all the remaining cerebellar nuclei as paleocerebellar, a subdivision which has been adopted in the present text. The neocerebellar part of the dentate nucleus projects entirely to the thalamus.

EXPERIMENTAL ANALYSIS OF CEREBELLAR FUNCTION

A. Complete ablation

Historically the functions of the cerebellum were first studied by analysis of the effects of removing the entire organ. The picture of grave motor disturbance which ensued after ablation will therefore be described first, and then the attempt will be made to analyze the disturbance in terms of more specific deficits that follow regional destruction of the primary divisions of the cerebellum. The principal disturbances are those of equilibrium, posture and volitional movement. Special terms have been used to describe these aberrations of movement and equilibrium, and it is essential first to define them.

Terminology. The essential disturbance of movement following cerebellar injury has been variously described as ataxia, incoördination and asynergia. The exact connotation of each of these terms is somewhat uncertain, and it is preferable, where possible, to describe each aberration of movement in a specific manner. However, some general term to embrace all the motor manifestations is essential, and the majority of authors have adopted either ataxia or asynergia. Ataxia has sometimes been confused with locomotor ataxia caused by destruction of the posterior roots, and since asynergia is more accurately descriptive in indicating a failure of harmonious action of synergic muscle groups — agonists, antagonists and fixating muscles — “asynergia” will be employed as a comprehensive term in the discussion that follows.

Other specific disturbances of movement can be defined as follows:

Dysmetria includes any disturbance in range of voluntary movements.

Hypermetria is excessive range of movement, *e.g.*, when a limb overshoots.

Hypometria is deficient range of movement in which the limb stops before the goal is reached. Frequently a concomitant factor is a disturbance of the force of movement which is not well adapted to its end.

Decomposition of movement represents the performance of an act so that "the various components of the act are not performed in their proper sequence or measure."

Tremor may be classified as an oscillating movement occurring in an extremity while maintaining a posture ("static tremor"), and that occurring during any part of active movement ("kinetic tremor") and in any place. Terminal tremor, *i.e.*, the tremor occurring at the end of a movement is usually more marked than the tremor at the start or during the course of a movement.

Tone (tonus or postural resistance) in clinical parlance refers "to that slight constant tension characteristic of healthy muscles." To the physiologist "tone" is a reflex postural contraction most evident in antigravity muscles, the degree of postural contraction in any given muscle depending upon the position of the body in space at the time of examination.

Hypotonia is a somewhat unsatisfactory but widely used term denoting a diminished resistance to passive movement; the passive movement of a "hypotonic" limb may be carried through a range greater than normal, and on passive shaking of the proximal segment of a "hypotonic" limb there is abnormal excursion at the affected joint.

In *fish*, removal of the cerebellum causes disturbances of swimming movements and of balance, effects generally interpreted as those of impairment of the vestibular mechanism; similar sequelae are seen in frogs (Mayer and Heldfond, 1936). In *birds*, the effects of ablation have been studied thoroughly by Lange (1891) and Bremer (1924, 1935), who report grave impairment of balance associated with marked increase in stretch and tendon reflexes; the latter reflex exaggeration causes the birds to walk stiff-legged on the tips of their talons. The effects are thus chiefly in the postural sphere, asynergia and tremor being much less conspicuous than in higher forms.

In *dog* and *cat*, removal of the cerebellum causes similar but more profound disturbances. The animals for some days are completely incapacitated and subject to periodic seizures of extensor opisthotonos similar to that seen in the decerebrate state. Modern study of such cerebellar ablations began with the work of Luciani (1891). He distinguished in dogs three phases in the recovery from complete cerebellar ablation which he designated "functional exaltation," "deficiency phenomena" and "compensation." Although this division into stages is somewhat arbitrary, his description of locomotor disturbances is accurate and will be described in Luciani's terms.

(i) *Period of functional exaltation.* During the first week or ten days after the cerebellum has been extirpated, the animal has periodic seizures of opisthotonos with head retraction and tonic extensor spasm of all the antigravity muscles. The posture of the animal is similar, except for its spasmodic fluctuations, to that in the decerebrate state, *i.e.*, the extensor spasm is at first marked and enduring. Luciani's cerebellar experiments were published in 1891 before Sherrington had described decerebrate rigidity, so the similarity between the two conditions was not apparent. Luciani was inclined to attribute the extensor spasm to irritation incident to operation. Sherrington (1900c, p. 908), however, interpreted Luciani's period of "functional exaltation" as a release phenomenon similar to decerebrate rigidity, and arising from interruption of cerebellar connections, principally from the anterior lobe and its nuclei (see below). This conclusion was strongly supported by the stimulation experiments of Miller and Banting (1922).

(ii) *Deficiency phenomena.* Within two days of decerebellation in the monkey, and after a week or ten days in dog and cat, the animal is able with some difficulty to execute voluntary movements. At this time it begins to exhibit three prominent symptoms, still referred to as the Luciani triad, *asthenia* or a weakness of the muscles, *atonia* or absence of the normal postural resistance of the skeletal musculature, and *astasia* or intention tremor with discontinuities of movements, dysmetria, etc. The significance of these symptoms will be discussed below.

(iii) *Compensation.* After a month the animal begins to propel itself on all fours, and during the next several months a marked, but gradual, amelioration occurs in the deficiency phenomena. Tremor becomes less marked as do *asthenia* and *atonia*.

More recent studies have tended to minimize the significance of Luciani's three stages, and some of the individual symptoms described by Luciani have been considerably elucidated. Sherrington pointed out that if in the decerebrate animal the cerebellum is removed, or the superior cerebellar peduncles cut, a marked increase in extensor rigidity occurs and the animal assumes an opisthotonoid posture with hyperextension of the neck muscles. Irritation of the cerebellar peduncles by section of them lower down does not increase the phenomenon; hence irritation must be ruled out as an explanation of the phenomenon. Furthermore, the signs of release of the postural mechanism persist indefinitely, for decerebellate animals, especially dogs, continue to show increased extensor reflexes in the form of exaggerated positive supporting reactions (Magnus and Rademaker, ch. x) as long as they survive. Stretch reflexes are also permanently augmented.

Luciani's "deficiency phenomena" of weakness, atonia and *astasia*, are all well recognized symptoms of extensive damage of the cerebellum. Weakness in volitional movement, *i.e.*, increased fatiguability of the affected muscles, is a conspicuous feature of cerebellar deficit in man. Atonia, or "hypotonia" as it is more accurately called, has been a disputed symptom since dogs and cats do not show it if their vestibular nuclei are not damaged by the cerebellar ablation. However, the higher primates all tend to show hypotonia following lesions restricted to the cerebellum, a point which will be discussed in the next section on functional localization. *Astasia*, or intention tremor, is a basic manifestation of extensive cerebellar destruction; indeed, discontinuities of volitional movement which take the form of coarse terminal tremor were among the earliest symptoms to be recognized.

Luciani's period of "compensation" continues for a matter of years. In some of Rademaker's dogs which have survived periods of three and four years after

decerebellation there has been detectable improvement in motor capacity for periods of well over two years.

Complete ablation of the cerebellum in *monkeys* has been carried out by a number of investigators and the general course is similar to that seen in dogs and cats (Fulton and Dow, 1937). Cerebellar tremor or astasia does not develop either in dog or monkey until the animal is sufficiently recovered to execute volitional movement. The monkey is generally moderately hypotonic after recovery from a cerebellar ablation and may show some increase in positive supporting reactions, although these are never so marked as in the dog. Decerebellate monkeys, like dogs, also have disturbances of balance with tremor and volitional movement. The question naturally arises whether the symptoms of complete ablation may not be sorted out into discrete syndromes referable to the major anatomical divisions of the cerebellum discussed above.

B. Functional localization in cerebellum

From the beginning of modern study of the cerebellum, there have been two opposed interpretations of its functions. With the discovery of the motor area of the cerebral cortex, all parts of the forebrain and cerebellum were faradically stimulated in the hope of securing further evidence of functional localization. Ferrier (1876; see also Ferrier and Turner, 1894) obtained from the cerebellum signs of electrical responsiveness of the eyes, head and neck, but responses were fickle and possibly due to escape of stimulating current. The idea of discrete localization of small muscle groups within the cerebellum gained support in 1906 when Bolk published his monograph on the mammalian cerebellum. He pointed out that in the giraffe the lobulus simplex was greatly enlarged and he inferred from this and other comparative evidence that the lobulus simplex regulates the neck musculature; in spider monkeys, the flocculus is greatly elongated and this Bolk correlated with the prehensile tail.* The cerebellar hemispheres, Bolk argued, developed along with increased complexity of movement of the extremities: the anterior part of the hemisphere (lobulus ansiformis) is therefore concerned with the upper extremity and the posterior part (lobulus paramedianus) with the lower extremity; the posterior vermis with the trunk musculature, the anterior vermis and lobulus simplex with the neck and head. Bolk's hypothesis proved attractive and has stimulated work both among physiologists and comparative anatomists, and the concept has not been disproved.

* The most exhaustive comparative study of the folia of the mammalian cerebellar cortex is that of H. A. Riley (1929). He describes the cerebella of the giraffe and spider monkey and of many other mammals.

The second interpretation of cerebellar function had its origin with Flourens(1824), who maintained that destruction of the cerebellum interrupted basic physiological functions such as equilibration, walking, etc., and that one could not regard the cerebellum or any of its parts as an instrument for regulation of specific anatomical entities. This point of view was stoutly championed by Luciani, who maintained that the cerebellum "functions as a whole," and that the only well-defined anatomical division of functions is in its bilaterality, each half presiding over the bodily musculature of the same side. In 1900, Sherrington (1900c) supported his point of view, remarking that "the reason that it 'functions' as a whole seems clearly because it is so largely a piece of mechanism that deals with the innervation, not of this or that piece of musculature, but of the musculature of the body as a whole." In other words, the cerebellum governs a specific physiological function, or possibly several specific functions, and its several parts do not control individual muscles.

Recent study of the phylogeny and embryological organization of the cerebellum, while tending to support the "unitarian" concept of cerebellar function, nevertheless has pointed to a type of *functional*, as opposed to an anatomical, localization, which is entirely compatible with the Luciani-Sherrington hypothesis. Indeed, Sherrington(1896, p. 382; 1898) was the first to point out that the anterior lobe of the cerebellum, when electrically excited, inhibits decerebrate rigidity; the response is specific to the anterior lobe and cannot be obtained from any other part of the cerebellum. This was independently confirmed by Loewenthal and Horsley(1897), and more recently by Miller and Banting(1922), Bremer(1924), Denny-Brown, Eccles and Liddell(1929). Comparative anatomical study indicates that the anterior lobe, through its spinocerebellar afferents and rubrospinal efferents, is equipped to preside over postural mechanisms. These studies also indicate that the flocculonodular lobe is equipped to influence vestibular mechanisms, the pyramis undoubtedly has some connection with organization of vision, and that the neocerebellum is concerned with the integration of volitional movement — all highly integrated functions and not anatomical entities. Observations on regional ablation and regional stimulation of these larger divisions of the cerebellum entirely substantiate comparative inferences concerning functional localization. The subject will be discussed under the following headings:(i) regional ablation

and stimulation of specific areas;(ii)the stimulation of specific nuclei; and(iii)section of individual cerebellar peduncles.

REGIONAL STUDIES OF CEREBELLAR CORTEX. Followers of Bolk maintained that isolated lesions of the cerebellar hemispheres have caused symptoms in individual muscle groups. Thus, lesions of the anterior lobe are said to have affected the neck and head musculature, lesions of lobulus ansiformis the musculature of the ipsilateral upper extremity and, curiously enough, nearly all, even Gordon Holmes, are agreed that lesions of the pyramis and uvula affect the trunk musculature. Regional stimulation of the cerebellum, beginning with Ferrier and supported by Mussen(1927), has been thought to support the inferences drawn from regional ablation by Bolk. But this is scarcely the case. Especially is this true of recent work on primate forms where, if discrete localization existed in the cerebellum, one would expect to find it more highly developed than in cats and dogs on which the earlier work was based. The problem of functional localization as studied in primates may be stated as follows.

Flocculonodular lobe. Ablation of the flocculonodular lobe, and of no other part of the cerebellum, causes conspicuous disturbance of equilibration unaccompanied by changes in reflexes or by tremor in volitional movement. Similar disturbances have been described by Groebbs(1928)from removal of the entire posterior part of the cerebellum of pigeons; Botterell and Fulton also saw a corresponding syndrome in monkeys following removal of nodulus, uvula and pyramis. Dow(1938)has shown unequivocally that the syndrome is due to destruction of the nodulus and flocculus; if the uvula is also involved, the syndrome is slightly more conspicuous; but isolated destruction of the pyramis, tuber or declive, or of any part of the anterior lobe(except the lingula), fails to cause disturbance of gait or balance, or to intensify the syndrome already produced by ablation of the nodulus. In the monkey and to a greater extent in the baboon and chimpanzee, isolated destruction of the nodulus causes symptoms persisting for a month or more, characterized by oscillation of head and neck, falling, so-called "ataxia of trunk" and a titubating abducted gait. During the first days after the lesion, the animal was reluctant to move, clung to the bars of the cage, generally in a corner, but when the trunk was thus motionless movements of the arms could be carried out without tremor and there was no evidence of hypotonia or reflex change. As further

evidence of the vestibular character of the disturbance, the nodulus was removed after bilateral destruction of the labyrinth. In these circumstances, there were no additional vestibular symptoms other than those already caused by labyrinthectomy. The significance of this so-called trunk ataxia will be discussed below when considering the clinical implications of physiological studies on the cerebellum.

Uvula and pyramis. Isolated removal of the uvula causes a transient disturbance of equilibrium lasting only a few days; but this is in keeping with the fact that the uvula receives a few projections from the vestibular nuclei. All parts of the skeletal musculature appear to be equally affected by the equilibratory disturbance, whether the uvula is removed or the nodulus. The responses of the uvula to stimulation have not been thoroughly investigated.

The pyramis, when removed as an isolated entity, causes, as already mentioned, no reflex disturbance or sign of impaired balance. The only symptom detected in three monkeys from which the pyramis was ablated was a rather surprising inability to arrest forward locomotion in time to prevent crashing headlong into a clearly visible obstruction. When set loose in a corridor, a monkey three or four days after the pyramis has been removed would run full force into a door at the end. The significance of this has not yet been established, although it is possibly to be correlated with the fact that the pyramis is the most responsive part of the cerebellum for eye movements. Faradic stimulation of the pyramis gives rise to upward movement of the eyes; and it is possible the pyramis may be concerned in some way with the integration of proprioceptive data essential for gauging distance (see Dow, 1935, 1938a).

Paraflocculus. This is a relatively silent area, forming a large part of the paleocerebellum, in which stimulation and isolated ablation have failed to reveal any discrete localization of function. It was once thought to be associated with the eye muscles, but well-controlled stimulation has failed to confirm this belief (Dow).

Anterior lobe. As already indicated, faradic stimulation of the anterior lobe in a normal animal inhibits extensor postures and in the decerebrate preparation causes profound inhibition of decerebrate rigidity. This has been confirmed in many animals of the vertebrate series, being most readily demonstrated in birds. After such an inhibition, there follows a marked rebound contraction, first described by Miller and Banting (1922) and later studied in detail by Bremer (1924) and Denny-Brown, *et al.* (1929). Weak stimulation of the anterior lobe may initially increase extensor postures, while strong stimulation produces inhibition. It was inferred from this that both excitatory and inhibitory elements influencing the postural mechanism must exist in the anterior lobe. *Ablation* of the anterior lobe causes conspicuous *release* of the postural mechanisms. In birds, Ten Cate and Bremer and Ley (1927) find that the stretch reflexes are augmented and that in the cat, positive

supporting reactions become exaggerated after destruction of the anterior lobe.

Gervase Connor's important disclosures concerning the localization within the anterior lobe of the cerebellum may best be given in his own words(Connor, 1941; Connor and German, 1941):

TOTAL ANTERIOR CEREBELLAR LOBE. "Total ablation of this region provokes a striking picture.(i) There are profound disturbances in the postural sphere characterized by an abnormal responsiveness in the anti-gravity muscles to all postural influences, whether local, segmental or general static in nature. There result an extreme opisthotonos, strongly hyperactive reflexes of stance(*Stutz*, *Hinkebein*, *Stemmbein* and *Schunkel* reflexes of Magnus and Rademaker), incoördination in all extremities and the neck, hyperactive and spreading deep tendon reflexes and well-defined lengthening and shortening reactions. Moreover, these postural deviations are conspicuously modified by labyrinthine and neck tonic influences. In addition, as the extreme extensor dominance wanes a coarse irregular tremor appears in the extremities and the neck, but only when these parts are actively involved in support.(ii) There is a similar release of the vasoconstrictor and vasodilator mechanisms, a 'vasomotor ataxia.' Both vasoconstriction and vasodilation are hypermetric in response to changes in the environmental temperature.(iii) The bladder and rectal smooth muscle reflexes are similarly hyperactive, as contrasted to their preoperative status. Piloerection is accentuated.

"Analysis of these postural deviations reveals that there are two fundamental disturbances:(i) a release of the local extensor proprioceptor mechanisms of the neck and extremities, and(ii) a similar direct release of the labyrinthine tonic influences. Thus, the extensor dominance persists in the extremities after neck deafferentation, labyrinthectomy and decortication and disappears only after deafferentation of the involved segments. That the labyrinthine tonic influences also are directly released is reflected in the fact that the augmented labyrinthine responses in the extremities and neck disappear after labyrinthectomy, but persist in spite of deafferentation of the more peripheral segments, the extremities and neck. Further analysis designates that there is resident within the anterior cerebellar lobe a more precise functional type of localization, in which each extremity, the neck and the labyrinths are discretely represented.

SPINAL (PALEOCEREBELLAR) ANTERIOR LOBE. "(i) *Ablation of culmen* alone provokes a complex of signs entirely similar in direction to those already described in the total anterior decerebellate preparation, but, strikingly, they are limited to the hindlegs, each of which is equally involved. The forelegs and the neck are unaffected. The syndrome of this region is characterized by a profound release of the antigravity muscles in the hindlegs, of such a nature that these muscles respond hyperactively to all extensor postural influences. The local static reflexes are conspicuously increased; thus, the positive supporting reaction(*Stütz* response) is strongly hyperactive and well-defined lengthening and shortening reactions are present. The segmental static responses are similarly released; the reflexes of stance, the *Schunkel*, *Hinkebein* and *Stemmbein* reactions are increased to such a degree that, in the hindlegs, the gait is crooked and weaving, the extremities exhibit marked errors in range, rate, force and direction and are placed inefficiently for smooth balance. Moreover, the strength of these postural responses is distinctly modified by general static influences; thus, the neck tonic and labyrinthine

thine tonic influences result in a further increase or decrease, appropriately, in each of these reactions. The deep tendon reflexes of the involved hindlegs are likewise hyperactive and spreading and can be modified by changes in the animal's position in space. This extensor release is significantly less in degree than that observed after total anterior decerebellation, for reasons which will be noted.

"Further restriction of the ablation to one lateral expansion of the culmen results in entirely similar signs but with their further *limitation to the ipsilateral hindleg alone*. There thus appears a complex of signs restricted solely to a *single extremity*.

"(ii) *Posterior centralis*, which possesses a definite hemispherical expansion, controls, similarly, the forelegs alone. Extirpation restricted to this region is followed by the signs already noted but they are now limited to both forelegs, each of which is equally involved. Further restriction of this ablation to one hemispherical expansion in this region provokes the same signs but, again, these are limited to a *single extremity*, the ipsilateral foreleg.

"(iii) *Anterior centralis*, a predominantly midline structure, presides in like manner over the neck extensors. The signs are limited to the neck and are somewhat more subtle than those already noted. There appears an increased extensor postural sensitivity in the neck muscles but a conspicuous opisthotonos fails to appear unless the 'released' neck muscles are further reflexly stimulated (see below).

VESTIBULAR (LINGULA) ANTERIOR LOBE. "(iv) Following pure lesions of the lingula the signs are such as to suggest 'release' of the labyrinthine tonic influences. Though disequilibrium is profound, local and segmental postural reflexes in the extremities are entirely normal provided support is afforded the animal's head. The labyrinthine tonic effects upon the extremities are, however, abnormally increased. The syndrome fails to appear after preliminary labyrinthectomy.

"(v) Results of combinations of these discrete ablations indicate that opisthotonos appears only when the neck extensors are released and, in addition, a tonic influence upon them is also increased above normal. Thus, the prime requisite is that the anterior centralis be removed; then, either the labyrinthine tonic influences must be released by lingular ablation (resulting, compositely, in an extreme opisthotonos), or the foreleg extensor influence upon the neck be released by posterior centralis removal (resulting, compositely, in a mild opisthotonos)."

Neocerebellum. The effects of stimulation and of isolated ablation of the cerebellar hemispheres have been much discussed. Faradic stimulation of the neocerebellum, except in transitional zones such as the lobulus simplex, is entirely without effect upon the skeletal musculature, in the anesthetized animal. With implanted electrodes, however, S. Clark (1939) has disclosed that certain immediate and also complex delayed reactions follow direct excitation of points scattered over the whole cerebellum. "Different large areas of the cerebellum respond to stimulation with patterns of movement having a recognizable specificity for the area." The movements described by Clark lack the isolated and explosive quality of those evoked from the motor area.

Rossi (1913, 1925) has pointed out that neocerebellar stimulation does

cause an alteration in the excitability of the motor area. This experiment has been repeated by Dusser de Barenne(1936), and Earl Walker (1938b) has found that neocerebellar stimulation causes marked alterations in the spontaneous action current rhythm in the motor area, and that paleocerebellar stimulation has no such effect. Evidently therefore the neocerebellum and the cerebral cortex interact in a manner that one would anticipate on the basis of their anatomical connections and parallel phylogenetic development.

Isolated *ablation* of the neocerebellum has been studied by nearly all investigators of the cerebellum. In cat and dog the effects are slight and the animals quickly recover from such a lesion. In the monkey ablations restricted to the cerebellar hemispheres cause a better defined syndrome characterized by disturbance of skilled movements and hypotonia. Tremor, however, is practically nonexistent so long as the dentate nuclei are not involved. It would seem from the more recent comparative work that all symptoms are more enduring and more readily analyzed in baboons than in monkeys, and are much more pronounced in chimpanzees than in baboons(Botterell and Fulton, 1938). Unilateral ablation of the cortex causes homolateral awkwardness, hypotonia and disturbance of gait. Defects are equally marked in upper and lower extremities, all symptoms lasting at most for about two weeks, disturbance of gait being the most enduring. When the ablation involves the dentate nuclei, all the disturbances are more enduring and they are associated in addition with noticeable tremor of voluntary movements. Simultaneous bilateral ablation restricted to the cortex is responsible for graver symptoms than a unilateral lesion, and is accompanied by gross disturbances of gait, *i.e.*, leaping, and an inability to arrest forward progression when an obstruction is in view. No evidence was found in these experiments for discrete localization of individual muscles and limbs.

In chimpanzees, the signs following small ablations of the neocerebellum are much more conspicuous and enduring than in baboon or monkey. Thus, after a small ablation of the posterior part of the cerebellar hemisphere, hypotonia will develop in the ipsilateral upper and lower extremities, the hypotonia being readily demonstrable over a period of several months. There were also slowness and awkwardness of movement, but no tremor in volitional movement. Some hypometria, however, was present(Botterell and Fulton, unpublished).

CEREBELLAR NUCLEI. As already indicated, the cerebellar nuclei fall into two groups made up of the dentate nucleus which is largely neocerebellar, and the paleocerebellar emboliform, globose, and fastigial nuclei, the fastigial being the oldest. Responses of the cerebellar nuclei have been studied by Miller and Laugh-ton(1928a&b), who removed the cortex of the cerebellum and stimulated the nuclear masses directly; and by Hare, Magoun and Ranson(1937) who used the Horsley-Clarke technique, both groups studying cats. Sachs and Fincher(1927) and Magoun, Hare and Ranson(1935) have also used the Horsley-Clarke technique for studying the excitability of cerebellar nuclei in monkeys. In cats the observations with both techniques are closely similar. Thus from *N. emboliformis* and *N. globosus* marked flexion of the ipsilateral foreleg can be evoked accompanied by inhibition of decerebrate rigidity in the contralateral foreleg; the ipsilateral hindleg at the same time becomes flexed, the body is curved and there may be ocular movements. *N. dentatus* has a higher threshold: from it with strong stimulation rapidly alternating flexion and extension are produced in the ipsilateral foreleg without much spreading of effect to the extremities. From *N. fastigius* strong flexion of both forelegs occurs, generally accompanied by flexion of the ipsilateral hindleg. The efferent pathway for dentate, emboliform and globose nuclei is the brachium conjunctivum and the rubrospinal tract. The reactions from the fastigial nuclei still occur after section of the superior cerebellar peduncle, but are abolished by section of Russell's uncinate fasciculus. All investigators are agreed that the responses of the cerebellar nuclei represent changes in posture, *i.e.*, they develop slowly and represent patterns of response(flexion of one foreleg and extension of the opposite, etc.). Another characteristic of the response of the lateral nuclei is prompt rebound contraction after withdrawal of the stimulus. This is also a feature of response of the anterior lobe.

SECTION OF CEREBELLAR PEDUNCLE. Cobb, Bailey and Holtz(1917) described inhibitory effects on decerebrate rigidity from stimulation of the superior peduncles similar to those obtained from the lateral cerebellar nuclei and from the anterior lobe. More significant are the results of section of the individual peduncles. When all three peduncles on one side are cut through, the connections from both the neo- and paleocerebellum are destroyed. A disturbing ipsilateral syndrome develops comprised of asynergia, gross tremor, accompanied in baboons and chimpanzees by an enduring hypotonia. Even after a year, locomotor movements are not normal, although the animal regains to a very considerable degree the capacity to use its extremities in a coördinated manner. However, tremor and fatiguability persist together with a fairly marked degree of hypotonia. The animal also suffers from disturbances of balance. A study of section of the individual peduncles has thrown more light on the subject.

Superior cerebellar peduncle. The syndrome which follows interruption of the brachium conjunctivum is similar to that following section of all three peduncles, but less severe, especially from the point of view of ultimate deficit; disturbance of balance, moreover, is minimal(Ferraro and Barrera, 1936a). Indeed, after six months, the macaque has little trace of tremor or hypotonia, but recognizable incoördination develops if the animal becomes fatigued. Walker and Botterell(1937) have compared the effects of unilateral and bilateral section of the superior peduncles in the macaque, reaching the following conclusions. Unilateral section of the superior cerebellar peduncle causes conspicuous asynergia with tremor, dysmetria, decomposition of movement, etc., as already described. Bilateral section of the peduncle is followed by a similar but much more severe and persistent asynergia, involving one or more extremities, but without disturbances of balance

or so-called "trunk ataxia." Nystagmus did not occur. Following partial section of the superior peduncle there appeared a mild and rapidly subsiding syndrome, which undoubtedly accounts for the results of those who maintain that the superior peduncle is not essential for orderly movement. Walker and Botterell emphasized that when one superior peduncle is severed compensation occurs through activities of the remaining cerebellar connections, especially through those passing in the superior peduncle on the opposite side.

Middle peduncle. Section of the middle peduncle is difficult technically and there are no wholly satisfactory accounts of a lesion accurately limited to the brachium pontis (see Turner, 1940). Rolling of the eyeballs and deviation of the eyes have been described, but these almost certainly are symptoms of injury to the vestibular nucleus.

Inferior cerebellar peduncle. The studies of Ferraro and Barrera (1936b) indicate that section of the inferior peduncle gives rise to vestibular disturbances similar to those caused by ablation of the flocculonodular lobe. Ferraro and Barrera have been able in their sections to separate the vestibular projection of the inferior peduncle from the projections arising in the fastigial nuclei. They designate the section interrupting the vestibular fibres as "intramedullary," and that involving Russell's uncinate fasciculus as "supramedullary." Section of the latter causes nystagmus toward the side of the lesion and some hypotonia, but, unlike the intramedullary section, there was no uncertainty of gait or disturbance of equilibrium.

RELATION OF CEREBELLUM TO CEREBRAL CORTEX

The study of cerebellar tremor, particularly its mode of onset after ablation of the cerebellum, indicates that it appears primarily during voluntary movement; if present during rest, it arises only in those attitudes which must be maintained by volitional effort. The extent of the tremor varies in almost direct proportion to the intensity of volitional innervation. It has been pointed out by Walshe (1927) that these manifestations of cerebellar deficit are actually not due to the cerebellum at all, but represent imperfect compensation by the cerebral cortex. It becomes a matter of some interest therefore to determine experimentally what the effect will be on cerebellar symptoms of lesions of the motor regions of the cerebral hemisphere.

Several experiments of this character were carried out by Luciani (1891). He stated that: "as soon as the so-called motor zone is destroyed on one or both sides the animal (dog) with half a cerebellum loses for a long time, or forever, the newly acquired capability of holding itself upright and walking without falling toward the affected side." D  mole (1927) collected a series of rare cases of congenital lesion of the cerebellum in which cerebellar symptoms were not conspicuous until they were brought out by subsequent lesion of the cerebral cortex. Implicit in Luciani's experiments and D  mole's human cases is the idea

that the cerebral hemispheres, particularly the frontal cortex, are capable of compensating in a measure for cerebellar deficit, particularly for those disturbances referable to destruction of the neocerebellum.

Rademaker removed the cerebellum from thalamic dogs and succeeded in maintaining such a decerebellate-thalamic preparation alive for 89 days (Sager, 1935); but in arranging the operations in that sequence he did not have opportunity of studying the effects of cortical lesions upon cerebellar symptomatology. Fulton, Liddell and Rioch (1932) removed the cerebral hemispheres, first from one side and then from the other, of decerebellate cats. In their experiments the hemiplegic extremity of a decerebellate preparation ceased to show tremor as soon as the hemisphere had been removed, even though it still exhibited vigorous reflex movements such as those essential for scratching. A slight degree of tremor might return to such an extremity after several months owing to innervation from the ipsilateral hemisphere. After both hemispheres had been removed the decerebellate-thalamic preparation exhibited vigorous running movements, scratching, *all without a trace of tremor*. However, the animal was unable to stand or to walk. Righting reflexes were active, and it tended to assume a horizontal position, holding its head upright, but the extremities were held in odd and purposeless postures. The animal thus exhibited cerebellar asynergia to a marked degree without tremor.

In monkeys more precise localization has been secured; thus Aring and Fulton (1936) found that in removal of the premotor area opposite to a hemidecerebellation cerebellar symptoms become augmented on the affected side; the symptoms are further augmented when the ipsilateral premotor area is removed. When the contralateral area 4 is destroyed and volitional movements are thus diminished, cerebellar tremor becomes correspondingly diminished. Tremor does not disappear, however, until areas 4 and 6 are completely ablated from both cerebral hemispheres. In these circumstances a preparation results, the motor status of which is entirely similar to the decerebellate thalamic cat.

The interpretation of the cerebral-cerebellar relationship is not simple. Rossi (1913) disclosed that neocerebellar stimulation enhances the excitability of the motor area, and Walker (1938a) finds, in harmony with this, that such stimulation alters the spontaneous action-current rhythm from area 4. One would anticipate that the pyramidal projections, through their pontine collaterals, would be concerned primarily with the neocerebellum, and that extrapyramidal cortical projections, which influence the postural mechanism, would be associated primarily with the anterior lobe and the paleocerebellar mechanisms. Dow (1942) and Dow and Anderson (1942) have found that stimulation at any point on the motor area of cats and monkeys causes a diffuse discharge

throughout the whole neocerebellum. Foci on the arm area tend to affect the anterior neocerebellum slightly more than the posterior, but evidence for a clear cut topographical interrelation was not obtained.

One thus conceives of phasic contractions mediated by the pyramidal system as depending upon a background of postural contraction which changes appropriately with each volitional act. In the absence of the corpus cerebelli postural reactions are seriously disturbed, and the background for operation of phasic volitional acts is lacking. When the premotor area is removed, the postural mechanism is still further disturbed with the result that volitional acts become even more difficult of execution than before. This, we believe, affords a reasonable explanation of the accentuation of cerebellar symptoms which occurs when the extrapyramidal projections from the cortex are disturbed. The apparent diminution of cerebellar symptoms after removal of area 4 is probably due solely to the withdrawal of voluntary innervation.

CLINICAL IMPLICATIONS

General discussion of the functions of the cerebellum can best be given through a brief account of disturbances produced by lesions of the cerebellum in man. There are at least two well-defined clinical syndromes referable to pathological lesions involving the cerebellum. In thus classifying the syndromes of the cerebellum, those of the superior and inferior cerebellar arteries are omitted since brain-stem structures are generally involved in such vascular accidents.

FLOCCULONODULAR SYNDROME. The medulloblastoma, a common malignant tumour of the cerebellum, arises just over the roof of the fourth ventricle and tends in the early stages of its growth to destroy midline structures belonging to the archi- and paleocerebellum. Such tumours are prone to occur in children, and the symptoms produced are strikingly similar from one case to the next. The child becomes unsteady on its feet, progresses with a broad base, often losing its balance and falling backwards. There is conspicuously little tremor of the extremities, and if the patient lies in bed with his trunk at rest there may be no trace of cerebellar incoördination in the movements of his arms or legs. This has led to the use of the phrase "trunk ataxia" in describing the syndrome; *i.e.*, when placed on their feet the movements of the trunk in such patients are not coördinated with the movements of the extremities. However, it is obvious that what is disturbed is the capacity

to maintain balance, a physiological function involving the entire musculature of the body. Hence, the phrase trunk ataxia is an inadequate and misleading designation.

The work of Dow and the pathological observations of Ostertag(1936) give fresh significance to the symptoms caused by these midline tumours. As indicated above, Dow's ablations of the nodulus give rise to disturbance of equilibrium, closely similar to that in the early stages of a cerebellar medulloblastoma. Ostertag has just reported that such midline tumours arise almost invariably in the nodulus itself, and that the nodulus, despite its phylogenetic antiquity, is the last part of the cerebellum to cease cellular differentiation in embryological development. No doubt this accounts for its predilection as a favourable site of tumour formation. Bailey, who with Cushing(1925) was the first to define the medulloblastoma as a pathological entity, and who has had a large experience with these midline tumours, points out that when allowed to develop they eventually destroy the nodulus, uvula and the midline cerebellar nuclei. Botterell and Fulton destroyed these selfsame structures, including the fastigial nuclei, in the macaque without producing tremor, even though a full blown flocculonodular syndrome is present.

Bailey also draws attention to Leri's(1916) case of a gunshot wound of the posterior vermis, which was accompanied by unsteadiness, titubation, vertigo and other signs of disturbed balance, and to the syndrome of paleocerebellar atrophy described by Marie, Foix and Alajouanine(1922). Patients with the latter syndrome complain of difficulty in walking, and examination reveals disturbed equilibrium with progression on a broad base, forward and backward oscillation, with deviation from side to side and a tendency to fall backwards. There was no tremor, but rather marked slurring of speech with a hesitant and monotonous voice; as with medulloblastomas, nystagmus was practically absent. Pathologically the cerebellum showed primary atrophy of the anterior lobe and posterior midline structures including the midline nuclei. The dentate and pontine nuclei, and the greater part of the neocerebellum remained intact.

Lesions restricted to the anterior lobe of the cerebellum have not been clearly defined as a clinical entity, although the appearance in cerebellar disease of the positive supporting reaction(Schwab, 1927) in a case of cerebellar tumour leads one to suspect involvement of the anterior lobe. Of much greater interest, however, with all its protean manifestations in the sphere of posture and movement, is the syndrome of the neocerebellum.

NEOCEREBELLAR SYNDROME. Long defined as a clinical entity, first named by Brouwer, and most accurately described in man by Gordon Holmes(1922), the neocerebellar syndrome varies in intensity in proportion to the size of the lesion and, more particularly, with the extent of involvement of the dentate and emboliform nuclei. The presenting symptoms may be briefly discussed.

Hypotonia. Comparative study in the primates has indicated that hy-

hypotonia becomes an increasingly prominent feature of neocerebellar lesions as the evolutionary scale is ascended, *i.e.*, more marked in man than in any other vertebrate. It occurs with lesions entirely restricted to the cortex of the cerebellum both in chimpanzee and in man (Gordon Holmes, 1922, p. 1179). Intensity of the hypotonia increases with the size of the cortical lesion, and it is probably augmented if the dentate nuclei are involved, though the latter point has not yet been definitely established. In distribution, the hypotonia is rather more conspicuous in proximal than in distal muscles, although it is likely to be very marked both in ankles and wrist. According to Holmes (1922), hypotonia is strictly unilateral and ordinarily does not affect the muscles of the face or the trunk. Hypotonicity of the skeletal muscles undoubtedly aggravates disturbances of movement (Walshe, 1921), but for many reasons hypotonia cannot be looked upon as the primary cause of movement disturbances.

Disorders of movement. The basic disturbance of extensive neocerebellar lesions lies in the irregularity of movement, principally of volitional movement, although, as Holmes points out (1922, p. 1232), sub-cortical integrations of the reflex and automatic type are undoubtedly also disturbed. The more common disorders of volitional movement may be described as follows.

a. Dysmetria. Excessive range of movement is perhaps the most easily recognized sign of cerebellar disorder. Thus when attempting to touch the nose with his finger a patient with a cerebellar lesion is likely to strike his cheek violently; a monkey raises his foot higher than is necessary from the ground in walking and an affected extremity is passively raised from a position of rest and when released it drops back violently on to the body of the subject.

b. Errors of direction. Not only does the limb tend to overshoot the mark or fall short thereof, but it may pass wide of its mark. If a patient is asked to trace a circle or geometrical figure in space with his finger, the finger follows a broken zigzag line with wide deviations at the angles (dysmetria). A more common error of direction is the phenomenon described by André-Thomas as "the decomposition of movement" (Holmes, 1922, p. 1234):

"If asked to bring his finger from above his head to the tip of his nose the patient may depress the arm at the shoulder before beginning to flex his elbow; and in placing his heel on the opposite knee he may complete the flexion of the hip before bending the knee, with the result that the heel is raised too high and then lowered to the knee. Some times this decomposition of movement seems to be a purposive device to control its irregularities: on attempting to feed himself the patient often fixes the elbow firmly to his side and then brings the spoon to his mouth by simply flexing his forearms. Others, in trying to touch an object, extend their arm or leg rigidly and then swing the limb from the shoulder or hip towards it. These types of deviation from the direct line occur in both slow

and rapid movements, but are usually more pronounced in the latter, chiefly since in them voluntary correction is less easy."

c. Disturbances of rate. In the chimpanzee, after a small lesion of the neocerebellum, the extremities on the same side lag behind the normal extremities in the execution of such rhythmic acts as are involved in walking and climbing. When obliged to feed with his affected extremities, movements designed to obtain a given morsel are initiated after an abnormal latency and are carried out with a deliberateness wholly foreign to the normal movement patterns of a hungry chimpanzee. Holmes describes the same phenomenon in man: thus "the commencement is frequently slower than normal and usually less uniform in rate; the speed at which it is carried out varies considerably, being frequently less during the whole movement no matter how strongly the patient is urged to hurry, but in other cases the limb is lunged out or projected like an inert body, and acquired in its course an abnormal velocity." The latter type of abnormality is also present in subhuman primates, generally after adaptation to a considerably larger lesion than that just mentioned in the chimpanzee.

d. Disturbances of force (weakness of movement). In addition to errors of range, direction and rate, there is likely to be marked disturbance in the force of volitional movement. This was recognized by Luciani in his insistence upon "asthenia" as a primary cerebellar symptom, and is particularly conspicuous following neocerebellar lesions in chimpanzees. In the first days after such a lesion climbing movements are not only slow, but prehension is impaired and the fingers frequently slip from the rungs of the cage because the grasp is not sufficiently forceful. Correlated with this is marked increase in the fatiguability of the affected extremities. When held aloft for a few minutes, the affected extremity begins to sag and may even drop, however actively the patient tends to keep it in that position. Corresponding phenomena are seen in animals when their hands are held outstretched for feeding.

Tremor. The coarse discontinuities in volitional movements were among the earliest signs to be associated with lesions of the cerebellum. In our experience tremor is not a sequel of lesions restricted to the cerebellar cortex. It does occur transiently when a lesion has affected part of the dentate nucleus and becomes an enduring entity when the lateral nuclear mass, including emboliform and probably globose, is also extensively involved; so that tremor is not, strictly speaking, an enduring part of the neocerebellar syndrome. In discussing the factors underlying tremor, Holmes states that the phenomenon results from irregularities in rate of muscle contraction, and that errors of range and direction which necessitate correction are also factors in its production. Holmes also points out significantly that with gunshot wounds of the hemispheres tremor as such was less conspicuous than in the cerebellar atrophies in which the deep nuclei are more extensively involved. Typically, the tremor of a cerebellar lesion is, unlike that of locomotor ataxia, not affected by closure of the eyes; and is predominantly *terminal*

in type, *i.e.*, it becomes accentuated at the end of a given movement when the attempt is being made accurately to reach a given objective. The tremor differs from the intention tremor of disseminated sclerosis (in which brain-stem structures are also involved) in that the oscillations are coarser and less decisive. Holmes remarks: "It is an invariable rule that the more component movements there are in any action, the more irregular that action is."

Other signs of incoördination. There are many tests designed to bring out evidences of cerebellar incoördination. The *finger-thumb* test, for example, is based on the fact that every normal person can readily approximate in rapid succession the tip of each finger onto the tip of the thumb by flexing the fingers in appropriate sequence and opposing the thumb. A patient with a lesion of the cerebellar hemisphere carries out such a manoeuvre slowly and awkwardly, and if the lesion is large may be quite unable to negotiate the movements at all. There are also the *finger-nose* and *finger-finger* tests, *i.e.*, in one the patient raises his elbow and is asked to bring his index to the tip of his nose, and in the other to approximate the tips of the index fingers in front of him with elbows raised. Errors of range, direction, rate and force of movement with accompanying tremor can be readily brought out by these simple tests. There is also Babinski's oft quoted test involving rapid pronation and supination of the forearm. The cerebellar patient carries out the movements slowly and awkwardly on the affected side, to which disability Babinski gave the name of *adiadochokinesis*. There are manifestations of similar disability in habitual acts such as shaking hands, applauding, tapping a table, etc. The extent to which the phenomenon of *adiadochokinesis* depends upon the cortex and deeper nuclei has not been determined. It certainly represents a profound degree of *asynergia* and in its more marked forms undoubtedly indicates extensive destruction of the neocerebellum and probably the underlying nuclei.

Nystagmus. Nystagmus is a much more prominent feature of cerebellar lesions in man than in lower animals. Although there is some limitation of eye movement for a time after complete ablation of the cerebellum, nystagmus does not occur on lateral deviation of the eye unless the vestibular nuclei have been involved. In man, nystagmus on lateral deviation, especially when it involves attempted fixation on a point, is found in the great majority of lesions of the cerebellum, except for those of posterior midline structures. In our experience, nystagmus is not seen in monkeys and chimpanzees following neocerebellar lesions; there has been evidence, however, of an inability to gauge distances, which in all probability is due to impairment of proprioceptive integration from the eye muscles. Gordon Holmes interprets the disturbance of eye movements in man as due to errors and range of movement, and he believes that it represents a basic incoördination of the eye movements similar to that which occurs in the skeletal muscles.

Sensory disturbance. Rolando and Flourens early pointed out that there were no gross sensory disturbances following lesions of the cerebellum. However, the cerebellum is in receipt of a vast sensory projection from the spinal cord, evidently proprioceptive in nature, and also a large sensory projection from the eighth nerve direct and from the vestibular nuclei. One would anticipate therefore that some phase of proprioceptive sensibility would be disturbed by removal of the cerebellum. Sensory *limens* are difficult to determine in animals, except by la-

borious training in discrimination problems. In man, however, Holmes reports that in no single instance in his large experience of cerebellar lesions has he ever found an alteration in cutaneous sensibility, or in the sense of position. Pressure sensibility seemed also to be unaltered. In the majority of cerebellar cases, however, there is one aberration of sensory integration, purely subjective, but undoubtedly significant. If such a patient "hefts" a weight it seems heavier in the affected extremity than in the normal. On closer study of the phenomenon, however, the capacity to discriminate *weight differences* proved to be unimpaired even though a given weight appeared subjectively heavier. It must be inferred from this that the enormous sensory projections to the cerebellum are largely, if not entirely, unrelated to conscious sensation, and that they must subserve unconscious proprioceptive adjustments.

FUNCTIONAL LOCALIZATION IN MAN. In all of Gordon Holmes' cases of lesions of the corpus cerebelli, there was no evidence of functional localization in respect of the extremities. Thus if the upper extremities showed errors of rate and range of movement, the lower extremities had corresponding errors in the same direction. If there was tremor in the lower extremity, it was also demonstrable to approximately the same degree in the upper. Experience with monkeys and chimpanzees has been completely in harmony with Holmes' clinical experience in this respect. Lesions restricted to the tuber and declive have not yet been studied in higher primates, and further work must be done upon the anterior lobe of these forms before it is possible to define a syndrome of the anterior lobe. With evidence available, it is safe to assume that when positive supporting reactions are exaggerated the anterior lobe is involved.

The phenomenon of trunk ataxia, so-called, seen with lesions of posterior midline structures, and evidently due to impairment of the flocculonodular lobe, is not a disturbance of the trunk muscles primarily, but of a physiological function, namely, that of equilibration which involves virtually the entire skeletal musculature.

It is conceivable that the muscles involved in visual coördination, *i.e.*, those of the neck and eye, may have discrete representation in or about the pyramis, but more detailed studies are needed concerning the effects of ablating the pyramis, its responses to electrical stimulation, and its anatomical connection with the cerebellar nuclei and brain-stem.

The coördination of speech has been variously localized in the cerebellum from lingula, lobulus simplex and even the back of the uvula and nodulus, but such localization has been based in large measure upon the *a priori* reasoning of Bolk and upon unconvincing responses to

stimulation of these structures. It would be more logical to believe that speech was integrated by the newer parts of the cerebellum since speech is one of the latest capacities to develop in evolutionary history. From clinical experience it is clear, however, that speech is not seriously affected except with very large lesions of the cerebellum affecting the deeper nuclei. There is no evidence of dominance of one side of the cerebellum in relation to the speech mechanism such as exists in the cerebral cortex (Stenvers, 1921). The disturbances of speech are looked upon as an asynergia of the many muscles involved in the act of speaking.

SUMMARY

Comparative anatomical studies of the cerebellum have lately made possible a satisfactory subdivision of the organ based on its embryological organization. These disclosures have given fresh impetus to the study of functional localization within this complex organ, and it now becomes possible more adequately to translate comparative anatomical facts into physiological language. Adopting the terminology developed by Larsell, the cerebellum has two primary divisions: a vestibular portion, the "flocculonodular lobe" and a spinocortical part, the "corpus cerebelli" which is enormously developed in higher vertebrates and man; these two parts are separated by the fissura posterolateralis. The corpus cerebelli is made up of an anterior lobe (lingula, centralis and culmen) and a posterior lobe comprising the neocerebellum (tuber, declive, lobuli simplex, ansiformis and paramedianis), and a midline paleocerebellar division (pyramis, uvula and paraflocculus). These general divisions are shown in figure 107. Conclusions concerning functional localization are as follows:

Isolated lesions of the *flocculonodular lobe* give rise to grave disturbances of equilibrium characterized by swaying, staggering, and titubation (so-called "trunk ataxia"), but there is no tremor or serious reflex disturbance. The syndrome is virtually identical with that seen in mid-line cerebellar tumours of childhood, which in many instances arise directly from the nodulus (Ostertag). Section of the inferior cerebellar peduncle causes similar symptoms.

Stimulation of the *anterior lobe*, or of the roof nuclei to which it projects, causes inhibition of antigravity posture on the side stimulated; whereas destruction of the anterior lobe releases the postural mechanisms causing increased stretch reflexes, augmentation of decerebrate

rigidity, increased positive supporting reactions, etc. Precise functional localization exists in the anterior lobe, the neck muscles and each extremity having individual representation(Connor).

Ablation of the *neocerebellum*, on the other hand, causes disturbances of volitional movements characterized primarily by errors of force and rate movements; if the dentate nuclei are extensively involved in the lesion, tremor develops accompanied by errors of range and direction of movement. Disturbances from neocerebellar lesions are more marked and more enduring in primates than in dogs and cats, and more conspicuous in anthropoids and man than in monkeys. Hypotonia may be equivocal in cats and monkeys after lesions of the *neocerebellum*, but in chimpanzees and man it is enduring and plays an important part in causing movement disturbances. With bilateral destruction of the *neocerebellum* all of the symptoms just mentioned are increased, especially when the dentate nuclei are involved; in these circumstances severe disturbances of progression movements develop characterized by leaping and inability to arrest forward progression in the face of an obstacle. The last symptom may be due to disturbance of distance perception.

All symptoms just mentioned are accentuated when the medial as well as the lateral nuclei of the cerebellum are involved. Ocular and speech disturbances which occur with lesions of the corpus cerebelli in man are regarded as the result of an asynergy of the eye and speech muscles similar to that causing disturbance in the skeletal musculature.

XXVI

THE NERVOUS SYSTEM AS A WHOLE: THE CONDITIONED REFLEX*

THE discussion of the conditioned reflex in the pages which follow is not exhaustive. Its aim, rather, is to tempt the reader beyond the boundaries of neurophysiology into the field of physiological psychology. Although contemporary theory in neurophysiology provides no adequate formulation of the known facts of behaviour as modified by experience, the convergence and final coalescence (Lashley, 1941) of physiology and psychology must be the practical goal of both sciences. Hysterical disorders of sensation and motion and the dysfunction of organs in the absence of demonstrable lesions are among the ubiquitous problems of clinical medicine. This practical consideration is sufficient justification for the following brief review.

THE METHOD OF THE CONDITIONED REFLEX

In 1902 Pavlov had a clear prevision of the aims of the investigation which was to occupy him for the ensuing thirty-four years. "In the course of our experiments it appeared that all the phenomena of adaptation which we saw in the salivary glands under *physiological* conditions, such, for instance, as the introduction of the stimulating substances into the buccal cavity, reappeared in exactly the same manner under the influence of *psychological* conditions — that is to say, when we merely drew the animal's attention to the substance in question. . . . It is quite clear that the activity of even such apparently insignificant organs as the salivary glands penetrates unconsciously into our everyday psychical conditions through sensations, desires, and thoughts which in their turn exert an influence on the work of the glands themselves. We see no reason why the same should not apply to the other organs of the body. It is, indeed, by means of such unconscious impressions that the usual physiological processes of our bodies are guided. . . . Further it is clear that the adaptation of the salivary glands is a phenomenon of the same order as that, for example, of the pancreas. Hence, if we could analyse step by step the adaptation in the latter organ, and if it be open to us to regard the process in the salivary glands as the more primitive form, we have here a clear physiological scheme for the study of the development

* By Dr. H. S. Liddell, Cornell University, Ithaca, N. Y. Received April 2, 1943, this chapter replaces chapter xxvi of the first edition, but it vindicates its final statement: "The elucidation of mental phenomena, normal and abnormal, remains the most challenging problem of neurophysiology." Dr. Liddell has accepted the challenge and is meeting it with conspicuous success. — J. F. F.

of psychological phenomena. Thus a way is open to us, even here, toward a synthetic study of the whole indivisible life" (Pavlov, 1902).

It will be remembered that in 1902 Pavlov had standardized a procedure for the training of the dogs employed in the many studies of digestion then in progress in his laboratory at the Institute of Experimental Medicine in St. Petersburg. The animals were taught to stand quietly on a table. Struggling was discouraged by loosely adjusted loops passing beneath the limbs from an overhead beam. This arrangement, designed for the experimenter's convenience in collecting secretion from the gastric fistula, exerted an influence on the dog's behaviour not fully appreciated by Pavlov. Later research, however, has proved this influence to be of first importance in determining the types of canine behaviour which he meticulously described and classified as varieties of conditioned reflex action.

The dog, habituated to the restrictions of the Pavlov frame, finds itself, as Gantt has graphically described the situation, encased in a psychical straitjacket. Its freedom of action is sharply curtailed and it largely relinquishes initiative in the experimental situation. Under these circumstances the psychical secretion of saliva follows the promise of food as inevitably as the reflex secretion follows upon the stimulation of the buccal cavity by the food itself if two requirements are met. The first is that signals indicating forthcoming food must be regularly reinforced by feeding and the second requirement is that no distractions be permitted during the testing period. Because of the intimacy which develops between the dog and the experimenter, Pavlov soon discovered that the principal source of uncontrollable distractions in the experiments on psychical secretion was the investigator himself. In order to bring the dog's environment under rigid experimental control it was necessary to isolate the animal and to devise means, not only of observing its salivation at a distance, but also of causing the stimuli associated with food or no food to act upon the dog's receptors without the experimenter's appearance upon the scene. Moreover, a feeding device operating by remote control to deliver fixed quantities of food to the dog during the experimental session met the requirement of inevitable reinforcement by food of the appropriate feeding signals in an environment where uncontrolled stimulation had been stringently reduced.

Although most of the experiments from Pavlov's Laboratory were designed to analyze in detail the psychical secretion of saliva based on expectation of food, many of the investigations were devoted to a similar analysis of psychical salivation in anticipation of the introduction of weak HCl into the buccal cavity. A curved tube cemented to the dog's cheek and connected with a reservoir in the control room permitted the experimenter to squirt small quantities of acid into the dog's mouth following the signals regularly associated with the irritation of the buccal mucosa.

In relinquishing the digestive system for behaviour as his main object of investigation Pavlov, "after persistent deliberation, after a considerable mental conflict, decided finally, in regard to the so-called psychical stimulation, to remain in the role of a pure physiologist" (Pavlov, 1928). In subsequent writings he repeatedly refers to his theory of conditioned reflex action as the outcome of this struggle. On the occasion of receiving the Nobel prize in 1904 he briefly formulated the new theory.

He contrasted the usual reflex secretion of saliva resulting from stimulation of the mouth cavity with the salivary secretion evoked by stimulation of other receptors such as eye or ear. Both instances of secretion are due to reflex action

and can be included in a framework of physiological description. The constancy of the usual physiological salivary reflex depends upon few conditions and may be regarded as unconditioned in contrast with the reflex effects brought from a distance to bear on the salivary glands. The latter exhibit fluctuation and depend upon many conditions. Pavlov proposed to name them "conditioned reflexes." The adequate stimuli for the unconditioned reflex consist of those properties of the food or irritating substance to which the saliva is physiologically adapted while for the conditioned reflex such accidental properties as color or form may be adequate stimuli if they serve as signals for the essential properties.

Since each conditioned reflex depends upon an unconditioned reflex "it must be assumed that the point of the central nervous system which during the unconditioned reflex becomes strongly stimulated, attracts to itself weaker impulses arriving simultaneously from the outer or inner worlds at other points of this system, *i.e.*, thanks to the unconditioned reflex, there is opened for all these stimulations a temporary path leading to the point of this reaction. The circumstances influencing the opening or closing of this path in the brain are the internal mechanisms of the action or of the inaction of the signalling properties of the objects" (Pavlov, 1928).

As the investigation of conditioned reflexes in the dog progressed Pavlov elaborated this simple drainage theory with the inclusion of such concepts as cortical excitation, inhibition, irradiation, concentration and induction. Although he believed that his analysis of the phenomena of conditioned reflex action contributed to the physiology of the cerebral hemispheres and although he planned many conditioning experiments involving neurosurgery he remained preoccupied with a cerebrum of his own vivid imagining. "If we could look through the skull into the brain of a consciously thinking person, and if the place of optimal excitability were luminous, then we should see playing over the cerebral surface, a bright spot with fantastic waving borders constantly fluctuating in size and form, surrounded by a darkness more or less deep, covering the rest of the hemispheres" (Pavlov, 1928).

Although Pavlov's theory has been critically discussed by physiologists (Howell, 1925; Beritoff, 1924) its influence on neurophysiology has been almost nil and at present it is of historical interest only. In sharp contrast to the ill fate of his theory Pavlov's method of the conditioned reflex has attained increasing importance in physiological psychology and experimental medicine. Improvements and modifications in conditioning technique in conjunction with its use in the study of the behaviour of a variety of mammals including man have resulted in an impressive body of well-tested facts. The import of this new knowledge for experimental medicine will be considered later.

In concluding this brief résumé of Pavlov's method and theory his classification of the phenomena of conditioned reflex action will be outlined since the nomenclature introduced by him has found general acceptance. If a neutral stimulus, *i.e.*, one which has no observable effect on the dog's salivary glands, such as a sound or a light, is shortly followed by food, after a few coincidences of the new stimulus and food the stimulus which always slightly precedes the act of feeding becomes a signal for food and its isolated action evokes secretion of saliva. The

neutral stimulus has become a *positive conditioned stimulus* and elicits a *simultaneous conditioned reflex*(see Table I).

TABLE I. *Development of a conditioned reflex to a sound of 637.5 vibrations per sec.*
(Evans, 1926)

NUMBER OF TIMES COMBINATION OF SOUND WITH FEEDING HAD BEEN PERFORMED	EXTENT OF REFLEX IN 30 SEC. NUMBER OF DROPS OF SALIVA	LATENT PERIOD OF THE REFLEX IN SEC.
I	0	—
9	18	15
15	30	4
31	65	2
41	69	1
51	64	2

The newly established conditioned reflex is unstable and may be inhibited. An unfamiliar stimulus shortly preceding or accompanying the conditioned stimulus distracts the animal(elicits an investigatory reflex) and partially or completely suppresses the conditioned reflex. Pavlov refers to this phenomenon as external inhibition(see Table II).

TABLE II. *External inhibition by extra stimulus*

The conditioned stimulus was a visual one. The extra stimulus was provided by playing a gramophone record for a few seconds. At first there is external inhibition, but it disappears rapidly on repetition of extra stimulus(Evans, 1926).

Strength of visual conditioned reflex = 100 per cent

Effect of gramophone, 1st application = 10

2nd = 50

3rd = 65

4th = 85

5th = 90

6th = 94

7th = 100

Even well-established positive conditioned reflexes are influenced by external inhibition, but to a lesser degree than the new conditioned reflex.

All positive conditioned reflexes are subject to internal inhibition if the conditioned stimulus is not reinforced by the unconditioned stimulus. If the signal for food is repeated but no food is given the conditioned reflex undergoes extinction.

The extinguished conditioned reflex will spontaneously recover but may be more easily extinguished again. Finally, the conditioned stimulus arouses no further salivation. It has become a *negative conditioned stimulus* and now elicits a *negative conditioned reflex*. During its action a distraction will lead to *external inhibition* of the *inhibitory conditioned reflex*(disinhibition)and saliva will again be secreted.

TABLE III. *Experimental extinction of conditioned reflex*

The conditioned stimulus was given without being followed by the unconditioned(Evans, 1926).

INTERVALS BETWEEN SUCCESSIVE APPLICATIONS OF CONDITIONED STIMULI	TIME NECESSARY FOR EXTINCTION OF REFLEX
2 minutes	15 minutes
4 minutes	20 minutes
8 minutes	54 minutes
16 minutes	not extinguished in 120 minutes

A delayed conditioned reflex is established by the action of the conditioned stimulus for a fixed period preceding its reinforcement by the unconditioned stimulus(Table IV). The longer the delay from the onset of the conditioned signal to the moment of reinforcement the longer

TABLE IV. *Delayed conditioned reflex*(to acid, Pavlov, 1927)

TIME	CONDITIONED STIMULUS	SECRETION IN DROPS FOR 30 SEC. PERIODS
3:12 P.M.	whistle	0, 0, 2, 2, 4, 4
3:25 P.M.	whistle	0, 0, 4, 3, 6, 6
3:40 P.M.	whistle	0, 0, 2, 2, 3, 6
9:50 A.M.	tactile	0, 0, 3, 7, 11, 19
10:03 A.M.	tactile	0, 0, 0, 5, 11, 13
10:15 A.M.	tactile & metronome	4, 7, 7, 3, 5, 9
10:30 A.M.	tactile	0, 0, 0, 3, 12, 14
11:46 A.M.	tactile	3*, 0, 0, 2, 4, 5
12:02 P.M.	tactile	0, 0, 0, 2, 6, 9

* At the 10th second the dog moved its leg, striking against a metal basin.

will be the latent period of the salivary reaction. Any distraction occurring during the latent period will, through disinhibition, lead to immediate salivary secretion(as in the tests at 10:15 and 11:46 in Table IV).

A trace conditioned reflex is established by a training procedure in which the conditioned stimulus is discontinued, and after a pause of fixed duration the unconditioned stimulus is presented. Salivary secretion then occurs not during the action of the conditioned stimulus but only during the pause preceding reinforcement(Table V).

The recently established conditioned reflex exhibits *generalization*. If the conditioned stimulus employed during training is the sound of a metronome, a buzzer, pure tone, or any sound may serve as conditioned stimulus. With repetition, however, the conditioned reflex acquires increasing specificity and can no longer be elicited by stimuli

TABLE V. *Trace conditioned reflex*(to acid, Pavlov, 1927)

TIME	CONDITIONED STIMULUS	I MINUTE TACTILE STIMULUS	I MINUTE PAUSE
12:40	tactile	0	0.5
12:50	tactile	0	10
1:15	tactile	0	11
1:27	tactile	0	14

differing greatly from the training stimulus. The limit of differentiation or discrimination between stimuli can only be achieved, however, by extinguishing through non-reinforcement the salivary conditioned reflexes to stimuli which more and more closely resemble the signal employed in the formation of the original positive conditioned reflex.

MODIFICATIONS AND APPLICATIONS OF CONDITIONING TECHNIQUE. Rapid progress in the investigation of conditioned reflexes has involved modifications of the classical technique and applications of the conditioning method to various mammals including man. The essential requirements of the method as employed by Pavlov are few. The animal is trained to assume a docile attitude. Spontaneous activity is sharply curtailed so that the animal remains quietly in the special frame or enclosure. This repression of spontaneous activity comes about gradually through habituation to the experimental situation. Arrangements are made for eliciting an unconditioned reaction at the experimenter's convenience (in psychological terms, an experimentally regulated incentive such as hunger or fear of punishment is provided). Inevitable reinforcement prevails. For example, signals which indicate forthcoming reward or punishment are duly followed by the appropriate consequence. The animal is shielded from distractions and, during its tests, is isolated from the experimenter and from other animals. Finally, the activity of at least one effector organ involved in the unconditioned reaction should be measured and if possible recorded. In the ideal situation a continuous graphic record of the conditioning tests will include a record of the application of conditioned and unconditioned stimuli together with the responses of the effector organs selected for observation.

Table VI indicates the physiological reactions upon the basis of which conditioned reflexes have been formed. Heart rate and blood pressure must be added to the list.

Although further studies of salivary conditioned reflexes in the dog have been undertaken in this country by Gantt(1937), James(1941), Anderson(1941) and Zener(1937), most of the recent research on conditioned salivation has been devoted to the solution of special problems in physiology and psychology. It has also been found possible to establish conditioned salivary reflexes in the pig (Sutherland, 1939; Marcuse and Moore, 1942) and in man (Finesinger and Sutherland, 1939). During the last decade, however, the study of chronic disturbances of behaviour resulting from conditioning has served as a unifying interest in focusing the work of a number of laboratories on this more general problem. These experimental neuroses, as Pavlov called them, will be discussed later.

The two most important changes in conditioning technique have been, first, the use of *skeletal muscle* as effector instead of the salivary gland, and second, the simultaneous registration of a number of physiological functions in the same

TABLE VI. *Unconditioned responses and stimuli used to elicit them*(Hilgard and Marquis, 1940)

1. GLANDULAR, SMOOTH MUSCLE, AND BLOOD RESPONSES:	
Salivation	Dry food; acid
Change in skin resistance	Electric shock
Pupillary reflex	Change in illumination
Gastrointestinal secretions	Food
Vasomotor reactions	Shock; thermal stimuli
Nausea, vomiting, etc.	Morphine
Immunity reactions	Injection of toxin, antigen
Diuresis	Increased water intake
2. RELATIVELY INVOLUNTARY RESPONSES IN STRIATE MUSCLE:	
Flexion reflex	Electric shock
Knee jerk	Patellar blow
Eyelid reflex	Shock; sound; air-puff
Eye movements	Rotation
Change in respiration	Electric shock
Change in pitch of voice	Electric shock
3. SEMI-VOLUNTARY AND VOLUNTARY RESPONSES:	
Withdrawal movements	Electric shock
Mouth opening, swallowing	Food
Locomotion	Shock
Instructed responses	Various
Previously conditioned responses	Various

conditioning experiment. Conditioned alterations of heart rate and of the movements of respirations have a strategic value because of the possibility of comparing these physiological functions in man and animals under conditions of stress.

A modification of Pavlov's method of particular interest to the neurophysiologist is illustrated in figure 110. A puff of air directed at the eye elicits closure of the lid. When a stimulus such as a light regularly precedes the puff of air by a fraction of a second a conditioned movement of the eyelid occurs in response to the light and, as is shown in the bottom record of figure 110, may lead to complete closure of the lid, preventing the puff of air from striking the cornea. Since this method may be employed in the study of conditioned reflexes in the rat(Hughes and Schlosberg, 1938), dog(Hilgard and Marquis, 1935), monkey and man(Hilgard and Marquis, 1936), it provides the physiologist with a refined technique for comparative study. Moreover, the precision with which latency and magnitude of response may be determined enhances its usefulness for the neurophysiologist in timing neural events. With the sluggish secretory reaction only relatively crude measures of time and magnitude are possible.

Dworkin, Seymour and Sutherland(1934)devised a method for studying conditioned feeding behaviour in the cat. The animal is confined to a small enclosure and at the appropriate signal learns to lift the cover of a box from which food may be obtained. Food is supplied only following the conditioned signal. This is an all-or-none method, since the lifting of the cover of the food box is recorded together with the application of the conditioned stimulus and the delivery of the food. It has proved useful, however, in the study of the physiology of hearing(Dworkin, 1934)and in the investigation of neurotic disturbances in the cat(Dworkin, 1939; Masserman, 1942b). Sutherland(1939)has employed the method in conditioning the pig.

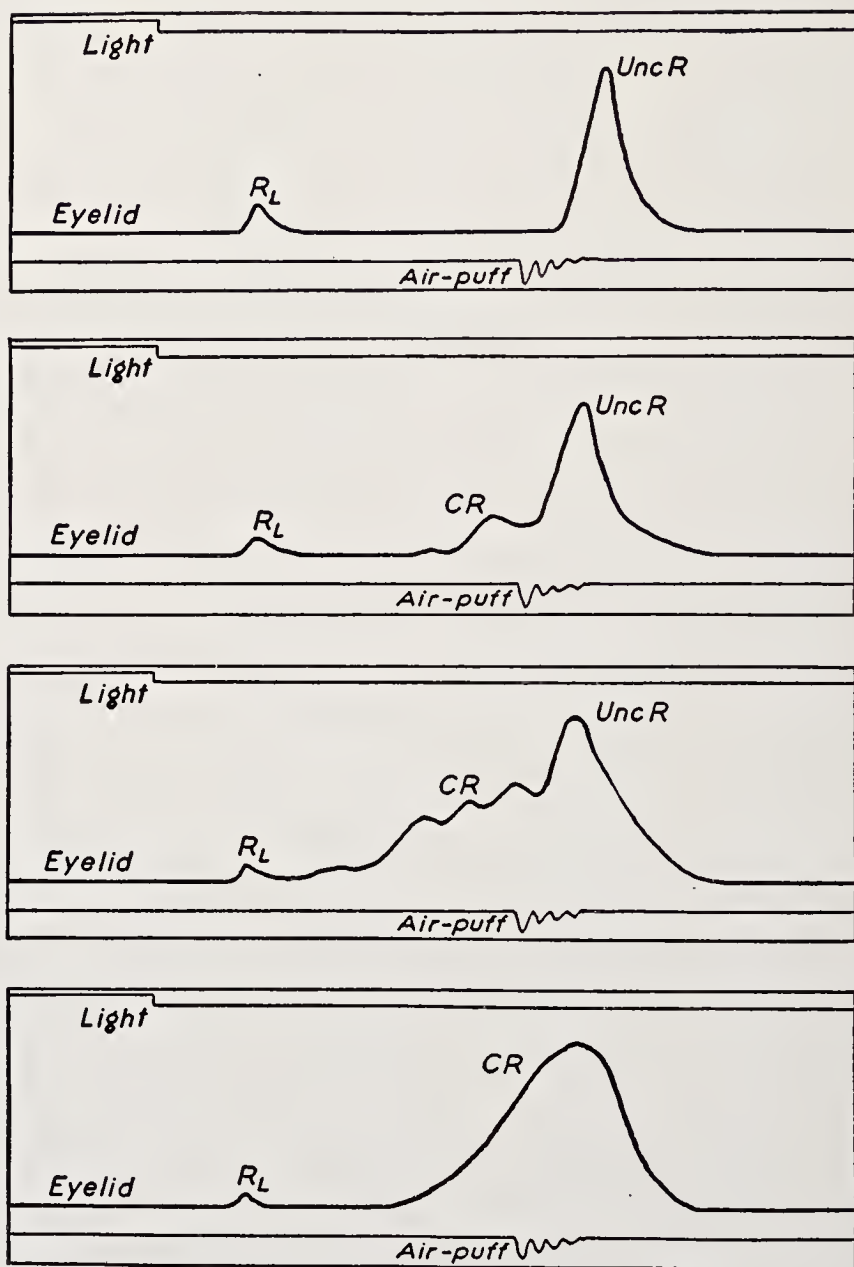


FIG. 110. Degree of resemblance of conditioned and unconditioned responses. The four records are tracings from photographic records of the eyelid responses of a single human subject. The top record shows the reflex to light (R_L) and the unconditioned response to the air-puff (UncR) before conditioning. In the second record the slight anticipatory conditioned response (CR) might be considered a reduced replica of the unconditioned response. In the third record, the irregularity and recruitment of the conditioned response differ markedly from the characteristics of the unconditioned response. In the final record, the complete lid closure prevents the air-puff from reaching the eye. At this stage, the response may be classified as an avoidance reaction. (From Hilgard and Marquis, 1940, p. 38.)

Space does not permit a description of the many methods of animal training which have been described as conditioning but which depart, often radically, from Pavlov's classical method. One example, however, will be given because of the extensive use which has been made of it in recent physiological and psychological research. The dog, habituated to the Pavlov frame, learns to avoid an electric shock by flexing its forelimb at an approaching signal. The shock is administered either through an electrically charged grid on which the paw rests, or through a bracelet attached to the limb. In other words, reinforcement of the conditioned stimulus is not inevitable since the animal may avoid the impending shock by the appropriate conditioned flexion of the limb (Culler, Finch, Girden and Brogden, 1935; Allen, 1942).

PRESENT STATUS OF THE CONDITIONED REFLEX

Pavlov regarded his study of conditioned reflexes as an investigation of the physiological activity of the cerebral cortex. At present, however, it must be recognized that although the method of the conditioned reflex may play a part in the study of sensory discrimination and learning and may be particularly useful in the analysis of various patterns of physiological function in relation to behaviour, its application to the problems of immediate interest to neurophysiologists is restricted.

Since 1895 physiologists have employed animal training procedures other than the method of the conditioned reflex in the analysis of cortical function.*

Even in the field of comparative psychology the usefulness of Pavlov's method is limited (Watson, 1914; Liddell, 1942b). In the recent literature the studies of cerebral function by Lashley, Jacobsen and their associates, in which training methods other than conditioning were employed give added evidence of the dispensability of Pavlov's classical method of the conditioned reflex for the successful investigation of the higher levels of neural function.

Nevertheless, through adherence to a fixed program of investigation,

* In a personal communication Donald G. Marquis says: "One of the earliest examples I have found of the use of training methods with study of brain functions is in a paper by Starlinger (1895), who trained one dog to give the paw after bilateral section of the pyramidal tracts at the level of the trapezoid body. Loeb (1901, p. 268) taught a dog to walk on its hind legs for food, which habit was retained after removal of the leg centers in both hemispheres. The most important studies in this field, however, are by Franz, Pavlov and Kalischer, who each apparently developed his methods independently of the others. Franz deserves credit for the first work by his study of the effect of frontal lobe removal on problem-box behaviour of cats (1902). Kalischer's first report was in 1907, in which he trained dogs in a differential food-taking reaction to tones. Kalischer, as you know, was very proud of his *dressurmethod* and in later papers sought to establish not only the superiority of his methods but their priority. He must, however, have known Pavlov's work and, at any rate, Romanes, Lloyd Morgan, Thorndike, and many others preceded him."

continued for 32 years with the aid of scores of collaborators, Pavlov, employing a simple method, accumulated and systematized an unprecedented body of easily verifiable facts concerning behaviour, an accomplishment which we may believe has given rise to a new field of experimental medicine more closely related to internal medicine than to neurology or psychiatry (Liddell, 1942a).

ACTIVITY OF INDIVIDUAL MOTOR UNITS DURING CONDITIONING. Hunter (1937) has observed the activity of individual motor units during the conditioning and extinguishing of a leg response to light stimulation in the white rat. The animal, restrained by a holder and with its legs fastened by slightly tensed rubber bands, was placed in an electrically shielded, semi-sound-proofed box. Electrodes from an inductorium were attached to the left hind foot and concentric needle electrodes were thrust into the gastrocnemius muscle of the same leg. Muscle potentials after suitable amplification were recorded from the cathode ray oscillograph. Motor conditioning was effected by paired stimulation of light followed by shock to the hind limb. Each exposure of the light lasted a second and the shock, beginning about $\frac{1}{2}$ second after the light was exposed, terminated with the light or just after it. About 200 stimulations were required to establish a stable conditioned reflex. Head and "squeal" responses were at times evoked by the light prior to any conditioned response of the gastrocnemius muscle. In some of the experiments the number of functional fibres in the tibial nerve was reduced by cutting and teasing. Hunter found that conditioning brought into activity individual motor units not before excited by the light. In some cases the conditioning increased the frequency of spontaneously firing units, a result not secured without such training. Moreover, the latency with which these effects were produced tended to decrease as conditioning progressed. In extinction the individual units dropped out, the conditioned speeding up of the spontaneously active units failed, and the latency of responses increased. With complete extinction, that is, when the light no longer elicited a response, pinching the animal reactivated some of the formerly conditioned units.

In a previous study Prosser and Hunter (1936) had observed a reflex startle response of the rat's hind limb to the click of a telegraph sounder. When the clicking was repeated at intervals of 10 seconds to 15 seconds the response weakened and disappeared. The extinction of this startle

response consisted of "a gradual diminution in the number of active motor units, a decrease in the duration of the after-discharge, but no change in latency for any units" (p. 617). These startle reactions, however, were found to differ from the conditioned responses of the gastrocnemius muscle in two fundamental respects. "The latency of the conditioned response is of an entirely different order of magnitude from that found in startle responses. And the latency of the conditioned response changes during conditioning and extinction whereas that of the startle response remains constant" (p. 624).

NEURAL STRUCTURES ESSENTIAL FOR CONDITIONING. In view of the results of a number of experimental studies since 1930 it must be concluded that the cerebral cortex is not essential for conditioning. Hilgard and Marquis (1940) in a recent monograph have thoroughly and critically reviewed the relevant investigations. They conclude: "The earlier insistence that the cortex was essential for conditioning has now given way before satisfactory evidence that conditioning may be mediated by subcortical structures. This has in turn made unnecessary the postulation of vicarious functioning to account for learning in the absence of given cortical areas. The cortex remains important in normal conditioning, and, according to the principle of functional encephalization, its importance increases throughout the phylogenetic series to man" (p. 335).

A brief description of the conditioned reflexes of two dogs after removal of the cerebral hemispheres (Lebedinskaia and Rosenthal, 1935; Culler and Mettler, 1934) illustrates the behavioural deficit resulting from this drastic operation. In both cases remnants of cortex were discovered at autopsy.

The dog studied by Lebedinskaia and Rosenthal lived without cerebral hemispheres for one year and two days. It maintained its weight and had an excellent coat. The salivary secretion to food and acid placed in its mouth was characteristic of normal dogs. Although it slept mostly at night it differed from normal dogs in sleeping for as long as 7½ hours without changing position. During sleep it was difficult to rouse it even by loud noises. It never attempted to find or choose a place to lie down and in the last few months slept in surprisingly uncomfortable positions. Waking instantly, it rose to its feet with ease and speed.

"Zavetny was not guided by vision. When moving about the room he walked into walls as if there were nothing in front of him, touched them with his front paws or nose, and only then changed his direction. In a large room with furniture he invariably walked into obstacles, and if his feet or head got entangled and stuck in an uncomfortable position, he did not try to free himself by a series of co-ordinated movements like a normal dog, but disentangled himself eventually after many fruitless attempts merely by accident, because in the mass of his disorganized movements there happened to be some which effected his release. If the dog, being hungry, accidentally walked into a basin of food, he would bite the edge of the basin until his nose came in contact with the food.

"The pupillary reflex took place when light was thrown into the dog's eyes.

"His taste reactions were normal; he immediately rejected meat damped with a solution of quinine, and would not drink milk containing 0.1 per cent of quinine, 5 per cent of common salt or 5 per cent of Liebig extract. Though movements of his head occurred which could be described as 'seeking' or 'sniffing' reactions, Zavetny failed to find pieces of meat placed in front of him even when he trod upon them. When Zavetny was demonstrated at Professor Orbeli's lecture and a piece of sausage was dangled in front of his nose, no reaction followed, but when the sausage was brought close to his lips, he ate it with an obvious appetite" (pp. 414-415).

When his paw was plunged into cold water he made no attempt to remove it, on one occasion for as long as 6 minutes. "Picking the dog up, putting him in the experimental stand, or preventing him from walking about on the floor provoked great excitement on his part and a display of strong motor reactions, panting and salivating, sometimes accompanied by biting and barking. However, he calmed down quickly when interference ceased" (p. 415).

The orienting reaction was present. "Cutting paper with a knife or winding a stop watch in the passage adjoining Zavetny's room caused him to raise his head and prick up his ears" (p. 416). This orienting reaction could be extinguished by repetition as in normal dogs. It was found possible to establish a conditioned salivary reflex to a metronome but only after 200 combinations of the metronome with food. Before this experiment, however, the dog was noticed "standing up on his hind legs and scratching the door leading into the passage where he was usually fed when we approached that door and he could hear our steps outside. We had never seen him before standing up on his hind legs or scratching the walls, and for a long time could not understand his behavior. The establishing of a conditioned reflex to the metronome explains it, however, as another alimentary conditioned reflex established to the sound of footsteps" (p. 417).

The decorticate dog described by Culler and Mettler was observed from July 20 to August 8, when the brain was prepared for macroscopic and microscopic examination. Although "only the loudest reports (pistol shot) were able to penetrate her apparent oblivion to environing stimuli and to elicit a mild startle" (p. 296), it was found possible to establish conditioned reflexes to doorbell and light with an electric shock applied to the foreleg as unconditioned stimulus. These reflexes were formed as rapidly as in the normal dog, but showed no refinement with practice. They remained to the end of training primitive escape patterns.

The conditioning method permitted the animal to avoid the shock by raising the paw. The decorticate dog, however, never learned to make the necessary precise avoiding movement. Instead, at the conditioned signal its behaviour as described by the authors was as follows:

“(a) Stiffening the forelimbs in a strong extensor-thrust, subject jerks the whole body back as far as the stock will permit head to come. This retraction of the trunk often raises both hind feet off the floor. (b) This is commonly succeeded by a strong rhythmic alternation of the hind limbs, hanging free in air. In other cases, both legs are strongly flexed and abducted into a kind of frog-like sprawl in mid-air. The left hind limb always introduces this pantomime and in general seems to dominate the right. (c) At other times the torso twists vigorously on the longitudinal axis, the left limbs (posterior always, anterior sometimes) flex and body sways toward the right. (d) Withdrawal of the forelegs usually comes rather late, if at all; the most important case being a kind of crossed reflex, left hindleg leading right foreleg in a rhythmic, swaying flexion of one or more terms. (e) The left forelimb enters the picture now and then by flexing late in the period. (f) When grosser activities fail, a mere catch or pause in breathing may be noticed. In most cases one or more of the above systems will dominate, with schematic simplicity and relief; then again nothing will occur save a mere hint or residue of the full activity” (1934).

The role of the *hypothalamus* in conditioning has been systematically explored by Masserman (1942a). Stimulation of the hypothalamus by means of an implanted electrode in the unanesthetized, freely moving cat elicits a fixed pattern of reaction involving piloerection, mydriasis, hissing, growling, lashing of the tail, clawing, biting and running movements. These reactions cease abruptly when the electrical stimulus ceases.

Visual and auditory stimuli were selected for conditioning experiments in which each of these agents was followed within a few seconds by a “sham rage” reaction from electrical stimulation of the hypothalamus. After 480 combinations of sound or light and hypothalamic stimulation over a period of 8 days, none of the 30 animals tested gave any indication of a pseudoaffective response to the preliminary sensory signal. Moreover, two cats which had been conditioned to open the cover of a food box in response to a light carried through the appropriate box opening at the signal in spite of the stimulation of the hypothalamus with the accompanying manifestations of sham rage.

Gantt and his co-workers have devised ingenious experiments to eliminate peripheral and central parts of the “conditioned reflex arc.” Loucks (1933, 1935) developed a simple method for electrical stimulation of the central nervous system in the unanesthetized animal. From a collodion-coated coil imbedded beneath the skin insulated wires lead

to the point to be stimulated. A primary coil connected to a thyratron generator is placed over the buried coil and the tissue at the electrodes is stimulated by the current induced in the buried coil. Gantt summarizes the experiments from his laboratory as follows:

"1. *Elimination of Efferent Structures.* In 4 dogs the right hindleg was paralyzed by crushing the anterior nerve roots between the exit from the lamina interna of the dura mater and the junction with the posterior root. Before regeneration of the injured motor nerves, elaboration of a simple conditioned reflex (withdrawal of the leg to electrical shock) was attempted on the paralyzed side, although the animal was, of course, unable to make the actual movement of the paralyzed limb. When the generalized conditioned response (minus its specific component) became well established, as shown by howling and motor defense reactions, the training was discontinued—in each dog before any evidence of regeneration. After regeneration the conditioned signal was given always without shock, and was followed by withdrawal of the formerly paralyzed leg—the appropriate and specific conditioned movement, but one which was never possible during the period of training [Light and Gantt, 1936].

"2. *Elimination of Afferent Structures.* (a) *Elimination of the Afferent Analyzer (Peripheral) of the Unconditioned Reflex:* A reflex movement of the hindleg was obtained by stimulating directly the dorsal root of a lumbar nerve. The stimulus was applied directly to the dorsal nerve to furnish the unconditioned reflex (movement of the leg), instead of, as in the usual experiment, applying shock to the skin of the leg to cause withdrawal. As in the ordinary conditioned reflex experiment, the shock to the dorsal root was preceded by a buzzing sound. After a few combinations the signal (buzzer) evoked the same movement as the induced shock to the dorsal root; that is, a conditioned reflex could be elaborated to a central excitation as easily as to the corresponding peripheral stimulus.

"Similar experiments were performed on 3 dogs using stimulation of the posterior columns of the spinal cord at about the level of the sixth lumbar nerve. The induction shock to the cord was preceded for one second by a conditioned stimulus (buzzer). The unconditioned reflex was a movement, usually flexion of the ipsilateral hindleg, to stimulation of the cord by the induction shock. In all these dogs there was a conditioned reflex to the buzzer, consisting of general tension plus movement of the hindleg, which appeared first on reinforcement 107 (6th day), reinforcement 120 (7th day) and reinforcement 422 (22nd day) in the 3 animals respectively [Gantt, 1937].

"Stimulation of the sigmoid gyrus to give a leg movement was performed in this laboratory by R. B. Loucks [1935]. In 3 dogs which received about 600 reinforcements of the conditioned stimulus with the faradic shock to the motor cortex, there was no evidence of the formation of a conditioned reflex.

"(b) *Elimination of the Afferent Member of the Conditioned Reflex:* The food-conditioned reflex was formed to stimulation of the area striata [Loucks, 1935]. Stimulation of the motor area of the cerebral cortex was used in the preceding experiments as a successful signal for the shock of the left foreleg" (Broden and Gantt, 1942).

In an investigation reported in this same article various movements evoked by stimulation of the *cerebellum* were successfully conditioned.

Electrodes from a coil imbedded beneath the skin over the temporal muscle were inserted in the cerebellum, their exact position being determined at autopsy. Three groups of responses were noted, *viz.*, movements of the ipsilateral limbs, contraction of the ipsilateral neck and shoulder muscles, and movements of ipsilateral eyelid and pinna. These responses, however, were neither uniform from animal to animal nor from time to time in the same animal. With shocks of moderate intensity they were executed without evidence of pain or emotional disturbance. "In general, when limb movements were evoked, the electrodes were found in the cortex or the subcortex of the medial aspect of the crus primum of the lobulus ansiformis. In some cases one electrode was in the vermis and the other in the crus primum" (Brogden and Gantt, 1942).

The second group of responses showed the widest variation in the character of the reaction and included opening of the mouth and raising of the larynx. In one animal, upon stimulation, rotation of the head toward the same side of the body was observed. In the case of the animal exhibiting this second group of responses the locus of the electrodes was the ventral aspect of the vermis, somewhat lateral to the midline.

Only two dogs showed responses of the third type. One reacted with sharp, complete closure of the ipsilateral eyelid. The locus of the electrodes in this case could not be determined. In the other dog the cerebellar stimulus elicited wigwagging of the ipsilateral pinna. The electrodes were later located in the vermis in the same general region as reported for the dog giving the second group of reactions.

An electric bell served as conditioned stimulus and was followed by the motor reaction elicited by the electric shock applied to the cerebellum. Gantt found that not all responses to stimulation of the cerebellum could be conditioned. The first and third groups of reactions were much more susceptible to conditioning than were those of the second group. Where conditioning occurred the motor response to the bell was firmly established in 2 or 3 test periods (40 to 60 trials). Positive and negative motor conditioned reflexes were as easily established by direct cerebellar stimulation as by the application of the electric shock to the skin of the leg.

In previous chapters the usefulness of the conditioned reflex method in neurophysiological research has been illustrated in discussing the

investigations of Allen on olfactory conditioning(ch. xvi), of Marquis and Hilgard on vision(ch. xvii), and of Culler and his co-workers on audition(ch. xviii).

VOLUNTARY AND INVOLUNTARY ACTION

The dog standing in the conditioning frame seems to have relinquished completely its spontaneity and to have become enslaved by the conditioned stimuli which the experimenter sees fit to employ. An incident related by Pavlov's colleague, P. S. Kupalov(personal communication)shows that the animal's reaction to the experimental situation is not wholly stereotyped. A dog had been conditioned to food by the sound of a metronome placed on a shelf above its head and by the hammer of a door bell tapping on the underside of the table on which it stood. Occasionally during intervals between conditioned stimuli it peered over the edge of the table as if reminded of the tapping or looked up toward the metronome, wagging its tail, licking its chops and salivating. Such anticipatory behaviour has been observed in our laboratory(unpublished observations)during experiments on conditioned motor reflexes to electric shock in the goat and pig, but not in the sheep. In the case of both goat and pig the animal gave the defensive reaction usually seen in response to the signal for forthcoming shock. The pig's behaviour suggested hallucination. It squealed and shook the foreleg as if to shake off the bracelet through which the shock was administered.

Pavlov emphasized the advantages of employing the parotid gland as effector organ in his investigation of the conditioned reflex(1928). We have seen in the preceding discussion of the neural locus of conditioning that a simple unequivocal effector reaction suffices to answer the experimenters' question as to the dispensability of a particular portion of the nervous system for the establishment or maintenance of a conditioned response. The majority of such experiments have employed skeletal muscle as the effector.

Moreover, the classical conditioned reflex method in which, through training, the animal has become the servant of the conditioned and unconditioned stimuli simplifies the experimenter's task of measuring accurately the latency, duration and magnitude of the responses elicited by the controlled stimulation. Modifications of Pavlov's method as in Hilgard and Marquis'(1936)blink reflex to a puff of air, and Hunter's

(1937) use of a single motor unit permit great refinement in measuring the temporal course of conditioned and unconditioned reactions.

However, the investigator, preoccupied with refined measurements of conditioned performance, may too easily come to regard the animal as a laboratory preparation. "The animal stands upon a table and repeatedly flexes a limb in anticipation of the shock which is to be applied to it. The mechanized routine of the experiments and the trained animal's apparently stereotyped response to this routine may lead the uncritical experimenter into a gross underestimate of the fundamental change which has occurred in the animal's orientation to its environment (past, present, and future). Actually, more is accomplished during conditioning than the immediate laboratory situation calls for" (Liddell, James and Anderson, 1934).

An experiment to illustrate the fundamental change in the animal's orientation consequent upon laboratory conditioning will be quoted from the same monograph. It shows how a sheep's seemingly voluntary behaviour in the barn is directly determined by its previous training in the laboratory. "The final stage in the development of the defensive reaction was clearly observed at the twenty-fifth presentation of food followed by shock. When the oats appeared the sheep promptly turned its head away from the pan, exhibited irregular, disturbed breathing, and executed a vigorous defensive reaction of the left foreleg to which the shock had been applied during training. The same defensive behavior at the appearance of the food dish was observed in the tests of the next day. At this time the experiments were concluded. . . . On the day following the final experiments in the conditioned reflex laboratory the animal's reaction to food was tested in the presence of the flock assembled in the barn. It now refused food offered under any circumstances. Thus, at feeding time, when the animals were in the barn and the experimenter appeared carrying a bucket of oats, the other sheep gathered about him and each one ate from the bucket when it was offered. The animal just conditioned against food, however, circled about the flock grouped around the pail and did not attempt to force its way to the oats for which the others were struggling. The experimenter now approached the animal, tempting it with the bucket of oats, but it ran briskly to the other end of the barn. The offer of a handful of oats likewise caused it to run away. The above attempts to feed this sheep were repeated on the next day with the same results. On the fifth day following the training in the laboratory it accepted food from the bucket or from the extended hand, although it showed slight hesitation. After that day its reaction to food appeared to be normal" (Liddell, James and Anderson, 1934).

In the human subject the well-established conditioned response of skeletal muscle resembles its voluntary contraction. Schlosberg (1928) succeeded in conditioning the patellar reflex in 44 out of 49 subjects, using as conditioned stimuli a bell, a click, a buzz and a tactual pressure. The conditioned knee jerks were very unstable and the subjects

varied considerably with respect both to rate of conditioning and to their ability to form a conditioned knee jerk.

"When facilitation, in the form of a voluntary response to the conditioning stimulus, was used, conditioned knee jerks were obtained more than twice as frequently as when no facilitating response was made. The records of the conditioned knee jerk resemble those of the voluntary contraction of the quadriceps group, and they both differ from those of the unconditioned knee jerk, chiefly in that the sudden initial rise seen in the latter is not found in the former. The latent period of the conditioned knee jerk varies between .2 and .5 seconds, being about the same as that of the voluntary contraction of the quadriceps group, and 5 or 10 times that of the unconditioned knee jerk" (Schlosberg, 1928).

Hilgard and Campbell(1936), in their study of the acquisition of conditioned eyelid responses in man, recorded an early stage in which the conditioned response to light resembles the reflex response to the air-puff on the cornea and later stages exhibiting irregularity and recruitment and complete lid closure(fig. 110), the latter closely resembling a voluntary wink. Hilgard and Humphreys(1938)found that the conditioned eyelid responses were influenced by voluntarily induced sets although conditioning could not be prevented by voluntary restraint.

In 1922 Cason succeeded in conditioning pupillary constriction in human subjects by pairing the sound of a bell with strong illumination of the eye. Eleven years later Hudgins(1933), beginning with simple conditioning of pupillary constriction and dilatation, arranged further experiments which enabled his subjects to achieve voluntary control of their pupillary reflexes. Of the 14 subjects who achieved such control 10 did not know that their pupillary reactions were being conditioned. The conditioning procedure was as follows: Pupillary constriction was first conditioned to a bell as in Cason's experiment. Then the subject squeezed a dynamometer to close the light and bell circuits and relaxed his grip in order to break these circuits. He squeezed and relaxed at the command of the experimenter. The next stage of training involved elimination of the bell and of the subject's hand responses, leaving only the experimenter's commands to contract and relax as the conditioned stimuli. The subject was then required to speak the words "contract" and "relax," to whisper them, and finally to say them to himself, signalling with a key as he did so.(It was shown that manipulating the key had no effect on the pupil.)

These pupillary responses to verbal stimuli showed no experimental extinction during the tests and were still present after an interval of 15

days. The latency of the conditioned constriction was found to be 5 to 10 times that of the reflex to light and its duration 3 to 5 times greater. Moreover, "the verbally controlled conditioned pupillary responses had that appearance of spontaneity and control by the organism which are so characteristic of the behavior called voluntary" (Hudgins, 1933).

In a theoretical appraisal of this experiment Hunter and Hudgins (1934) comment as follows:

"We are of the opinion that the attempted classification of behavior into voluntary and non-voluntary forms of response is of less significance than a classification of the corresponding behavior in terms of genesis, type of control, and temporal characteristics. An adequate account of what the psychologist has called voluntary action cannot as yet be given because the necessary experimental data have not yet been secured; but the hypothesis is offered that so-called voluntary behavior is essentially a conditioned response having a characteristic latency and temporal course and under the control of self-excited receptor processes."

The problem of distinguishing voluntary from involuntary action seems properly to belong to the class of problems derived from philosophical considerations. The experimenter interested in the behaviour of an individual mammal recognizes that this individual will, if given the opportunity, react by intention rather than from immediate necessity. That is to say, it will attempt to anticipate what is to happen in the light of its recent and remote past. Publications in the field of psychosomatic medicine (Dunbar, 1938; Liddell, 1941) illustrate the manifold dysfunctions which result from faulty anticipations based upon the arousal of previously experienced confusions, frustrations, and conflicts.

INTEGRATION OF PHYSIOLOGICAL FUNCTIONS IN CONDITIONING

In the preface to the first edition of this monograph one reads: "When, therefore, the intact nervous system is visualized, a mental picture is conjured up of two great interlacing systems — which share some receptors in common but which have others that are specific — and which discharge together in a synergic manner that makes for unification of reaction in the organism as a whole." The integrative action of these great interlacing systems can be effectively explored by means of Pavlov's classical method. This exploration is, in fact, so facilitated by the self-imposed restraint of the animal in the conditioning frame that the sampling of the motor and secretory functions participating in conditioned reflex action may constitute the unique contribution which the method of the conditioned reflex can make to neurophysiology. Not

only can patterns of physiological function be graphed and measured, but also the dependence of these patterns upon the individual's past experiences can be specifically determined. Study of the natural history of an animal's conditioned reflexes then leads the investigator beyond the physiology of the nervous system into the field of physiological psychology. Pavlov's reluctance to make this inevitable transition was the occasion for the previously mentioned "considerable mental conflict" which he experienced.

Our understanding of the nervous system will speedily increase when both physiologist and psychologist acquire, through practice, facility in ignoring the imaginary barrier between the two sciences. The general practitioner, internist and clinical neurologist must, of necessity, ignore the philosophical subtleties of the mind-body dichotomy in dealing at once and together with signs and symptoms. Even a brief survey of the many conditioned physiological functions which have been studied would unduly lengthen this chapter. I have, therefore, selected for cursory discussion only a few studies to illustrate the use of conditioning in the analysis of physiological patterns in behaviour.

CARDIAC CONDITIONING. A classical study of conditioned cardiac inhibition by C. S. Sherrington(1900), hitherto overlooked in reviews of the conditioned reflex, is of equal importance with Pavlov's first experimental studies of psychical secretion. I think it appropriate to quote at length from Sherrington's description of a conditioned cardio-inhibitory reflex in the dog:

"In a young dog under deep chloroform narcosis, I had performed a spinal transection close behind the origin of the phrenic nerves. Six weeks later, the trauma having completely healed and the condition of spinal shock having largely subsided, I placed the animal once more under chloroform, but this time not profoundly. I connected the femoral artery with the mercurial kymograph and proceeded to record the arterial pressure, allowing the chloroformisation gradually to pass off. As the depth of the narcosis waned, the breathing became quicker and less regular. The waking of the animal was accompanied by no pain, because the whole body was insentient behind the cervical region, and the kymograph attachment was in the femoral region. I was intending to faradise a branch of one of the nerves of the right hind limb. Inductorium, electrodes, galvanic cells, and whole electric circuit stood on a table near, but not on that on which the kymograph observation was in process. In order to be sure that all was ready, I closed the electric key and touched the vibrator of the inductorium. The harsh rattling noise of the vibrator lasted a few seconds, and I then stopped it by re-opening the key. Turning thereupon toward the arterial record, I was a little disappointed to see that a marked oscillation had suddenly upset the already somewhat undesirably irregular line that had to serve as starting level for the vaso-

motor reflexes I was wishful to study. It was clear that one would have to wait for greater quietude to re-establish itself again. I waited; the disturbance of the arterial pressure subsided; the previous fairly equable cardiac beat, despite somewhat disquiet respiration, returned. A few minutes later I again started, by force of habit, trying the inductorium for a couple of seconds preparatory to proceeding to excite and observe the vasomotor reflexes. Again, on turning toward the trace

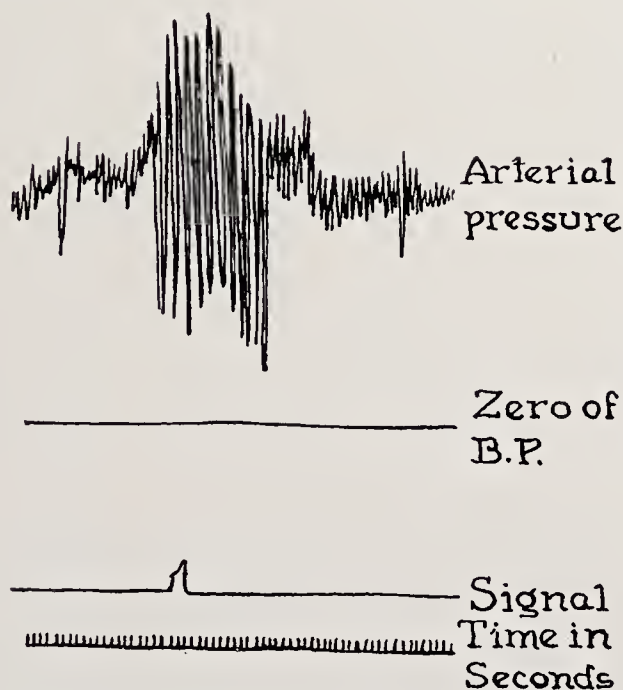


FIG. 111. Record of arterial pressure in dog 41 days after spinal transection at 7th cervical segment. Arterial pressure is high and good in spite of transection, the period of vasomotor shock having passed by. For the short period marked by signal, noise of vibrator of an inductorium sounded and was heard by the animal. The point of the signal marked nearly 8 mm. further to right than did kymograph pen. Inhibition of heart is shown by oscillations on kymograph trace. The line marked Zero of B.P. signified height of zero of manometer recording arterial pressure (Sherrington, 1900a).

running on the kymograph, I was met by a sudden disturbance that had altered it. This time it occurred to me that the sudden whirring noise of the magnetic interruptor might have caused the reaction. This supposition I proceeded to test, and soon found that each time the noise was repeated the disturbance of the circulation followed [fig. 111]. If the reaction had become less, as it frequently did after a number of repetitions, it was only necessary to wait for ten minutes or a quarter of an hour in order to re-obtain it in its original extent.

"I then remembered that in examining the limits of the cutaneous anaesthesia in this animal from week to week, I had at several times employed the inductorium; sometimes the electrodes had in making the delimitation been applied to points of skin still sentient, and no doubt had there caused sensations of unpleasant quality. The recurrence of the sound to the awakening animal occasioned now emotional anxiety. But in this animal the vasomotor centre cut off by the

spinal section from practically the whole of the rest of the vasomotor mechanism was quite unable to affect the arterial pressure. Hence that rise of pressure observed by Couty and Charpentier to occur under emotion of fear was impossible in this case. All the more obvious and uncomplicated for that reason appeared the inhibitory action exerted on the heart. The heart that had been beating at the rate of 180 per minute, suddenly fell for twenty seconds to a rate of 54 per minute. The respiratory rhythm was easily seen to be also altered, but no graphic record of the respiratory movement was being employed. A slight elevation of the mean arterial tension immediately preceding the vagus action on the heart I incline to attribute to mechanical effect on the circulation, secondary to alteration in respiratory movement. The interest of the observation here is that it gives an objective illustration of a disturbance emotional in character occurring in an animal after the possibility of vasomotor reaction had been set aside, and after the vastly larger portion of all visceral reaction had also been removed" (pp. 393-396).

Figure 111 reproduces Sherrington's kymograph tracing of conditioned cardiac inhibition. Sherrington had visited Pavlov's Laboratory and witnessed there the experiments on conditioned reflex action. It is interesting that he neither extended the observations just quoted nor discussed them in relation to Pavlov's work in his later analysis of the integrative action of the nervous system.

The conditioning of other cardiovascular functions has been demonstrated. Anderson and Parmenter (1941) carried out an extensive investigation of conditioned cardiac acceleration in normal and experimentally neurotic sheep (fig. 112). Gantt (Gantt and Hoffman, 1940) has observed the heart rates accompanying stable conditioned food reflexes elaborated 3 to 6 years previously and the cardiac responses associated with newly formed conditioned food reactions. During the 10-second action of the conditioned stimulus all animals showed an increased heart rate, in one case from 81 to 110 beats per minute. Slight increases in heart rate were also observed during conditioned inhibitions, in one animal from 82 to 88 beats per minute.

Psychical influences on the vasomotor rhythm of the spleen and on the splenic reflex have been observed by Hargis and Mann (1925). The dog's spleen was encased in a plethysmograph made of non-flexible collodion which remained in the abdominal cavity for long periods of time. The dogs soon became accustomed to the laboratory surroundings and acquired the ability to lie quietly on a table while graphic records were being made. In recording the rhythmic changes in the volume of the spleen the authors demonstrated the psychic effect of tempting the hungry dog with food. "While the animals, after having fasted for

18 hours, were having the preliminary tracings taken, meat was very quietly placed by an assistant where the animals could inhale the odor. The undulations of the fasting stage were replaced by waves of shorter duration and lesser amplitude which continued for a variable period of from a few to several minutes."

They also observed, in the first animal of their series, that when anyone entered the room the dog responded by an instantaneous momen-

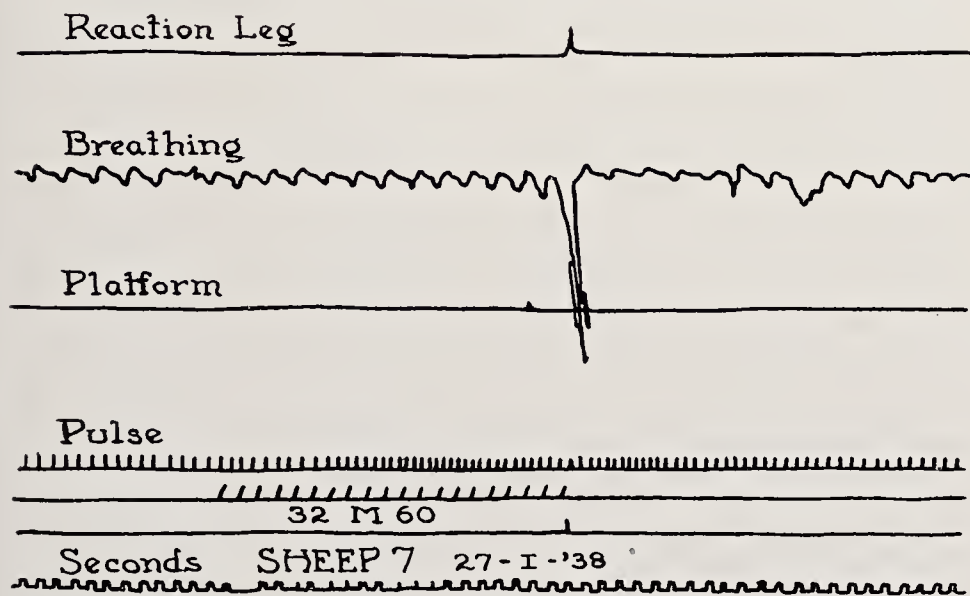


FIG. 112. A graphic record showing the absence of conditioned motor reflex in a sheep with an inhibitory form of experimental neurosis. Note, however, that although metronome followed by shock failed to evoke neuromuscular reaction, it elicited marked acceleration of pulse (Anderson and Parmenter, 1941).

tary decrease in the volume of the spleen, usually followed by an increase in the rhythmic changes in volume. This phenomenon was termed the splenic reflex. It was elicited by a wide variety of stimuli such as clapping of the hands, the sudden starting of a motor, the ringing of the telephone, pinching the animal's tail, or applying drops of cold water to its abdomen. This reflex was observed in every animal studied. In many cases the reflex was so readily elicited that the effect of diet and drugs was studied with the greatest difficulty. It often became necessary to carry on the observations in a closed room or at night when the laboratory was quiet. As in the case of salivary conditioned reflexes, the ease with which the splenic reflex was elicited depended

upon the type of dog. In the phlegmatic dog a vigorous splenic reflex occurred to each kind of stimulus the first time it was applied, but never twice to the same stimulus. In the unstable, nervous type, however, marked decreases in splenic volume were observed in response to almost all kinds of external stimuli no matter how often repeated, even though the animal appeared unconscious of the stimulus eliciting the change in volume of the spleen.

Menzies(1937) successfully conditioned *vasoconstriction* and *vasodilatation* in 12 out of 14 human subjects. The unconditioned reactions were aroused by dipping one hand in ice water or in warm water. A thermopile and high-sensitivity galvanometer permitted the recording of slight changes of temperature in the other hand. Stimuli such as bell, buzzer, words or nonsense syllables spoken by the experimenter, or the subject's whispered repetition of a nonsense word became effective as conditioned stimuli after 9 to 36 combinations of conditioned and unconditioned stimulation. In one case conditioning was present after a rest period of 92 days. In these experiments changes in skin temperature with excitement, anxiety, affectively toned thinking, drowsiness, mild fatigue and protracted fixation of attention had to be allowed for in interpreting the results of the conditioning procedures.

The *galvanic skin reflex* to a mild electric shock has been conditioned in animals such as the sheep and goat(Liddell, James and Anderson, 1934). Instances of conditioning in the human subject are described in the following studies: Bass and Hull(1934), employing the conditioned galvanic skin reflex to tactual stimulations of various regions of the skin, confirmed Pavlov's report on the irradiation of tactile conditioned reflexes in the dog. Switzer(1934)studied the properties of the delayed conditioned galvanic skin reflex in the human subject and Cook and Harris(1937)found that a stable conditioned galvanic skin response was obtained by warning the subject that an electric shock would follow a green light and that this response was weakened or completely eliminated by reassuring the subject that a shock would no longer follow the light.

A discussion of the conditioning of the functions of the gastrointestinal and genitourinary systems will not be attempted. For further information concerning the conditioning of visceral activities the reader may consult three authoritative reviews of the literature on the conditioned reflex by Hull(1934), Razran(1933), and Hilgard and Marquis(1940).

Investigators of conditioned reflex action will agree with the point of view expressed by Menzies(1937). "It will not be sufficient simply to establish the fact as to whether or not certain processes may be conditioned. The characteristics of the conditioned behavior must be discovered in each case. It is not justifiable to conclude cavalierly that all conditioning follows the principles of conditioned salivation in dogs. The experimental evidence already available indicates that this is not the case, but rather that different organisms and different response systems within the same organism present their own peculiarities of conditioning "(p. 75).

A peculiarity of the conditioned movements of respiration is their extreme sensitivity and brief latency in response to conditioned stimulation. Allen(1942), whose modification of Pavlov's method of the conditioned reflex has been previously mentioned, has recently recorded the changes in thoracic respiration in comparing the responses to positive and negative auditory, olfactory, general cutaneous and optic conditioned stimuli. The motor response was flexion of the right foreleg and correct responses were rewarded while errors were punished. At the positive conditioned stimulus the dog was required to flex the limb within 7 or 8 sec. in order to avoid the shock. If the leg was flexed at the negative signal the dog was whipped or scolded according to its temperament. The respiratory tracings indicated correct or incorrect conditioned responses when positive and negative signals followed one another at intervals varying from 2 sec. to 2 min. A series of alternate negative and positive conditioned responses with their corresponding respiratory patterns correctly corresponded to the conditioned stimuli when the tests were only a few sec. apart. The delicacy of the thoracic respiration as an indicator of positive and negative conditioned reflex action is shown in Allen's(1942)first figure.

THE EXPERIMENTAL NEUROSIS

Pavlov had early intimations of the pathological significance of the frame in which his dogs were confined because of the atypical reactions of some of the animals to this mild restriction of liberty. For example, one dog exhibited a "reflex of freedom." It could not remain quiet in the frame but struggled and panted until released, when it immediately became calm and often lay down near the experimenter. The behaviour of another dog was characterized by almost complete immobility in

the frame. This extreme docility was attributed to the influence of a "reflex of slavery." *

Moreover, other animals presented special problems which focused attention upon the peculiarities of the conditioned reflex method. Two dogs exhibited an exaggerated "guarding reflex" (Pavlov, 1928). A person, even well known to the animal, upon entering the room during the conditioning experiments, evoked aggressive behaviour, especially if he approached or touched the experimenter. Outside the room the same visitor could threaten or even strike the experimenter with impunity. The dog gave no suggestion of its previous aggressive behaviour.

In later experiments employing thermal stimuli as signals in conditioning, the animals so frequently fell asleep that Pavlov's co-workers were loth to undertake investigations involving temperature stimulation (Pavlov, 1928). It was also noted that dogs were spoiled for further study if conditioning were confined to stimuli of one sensory modality, e.g., tactile. It became the usual practice to establish in each dog a variety of conditioned reflexes to auditory, visual and tactile stimuli.†

In view of these findings Pavlov was perhaps unknowingly prepared to place a special emphasis upon the experiment of Shenger-Krestovnikova (Pavlov, 1927). In this experiment a dog was required to distinguish between a luminous circle as a signal for food and an oval of equal area and brightness as a signal for no food. As the oval approximated the circle more and more closely the animal distinguished between them until the semi-axes of the oval attained a ratio of 8 to 9.

* In one of the dogs (Melja) with a fistula, who was required to stand in the usual frame continuously for 7 to 8 hours, the author noted the following novel peculiarity of behaviour. Throughout the many hours of standing Melja astonished all those present by his almost complete immobility. In contrast to other dogs, he did not show signs of an over-full bladder which always occurred under the conditions of the investigation. On the other hand, after being freed from the frame, this dog, unlike the others, reacted so violently that he threw over the frame and tore all the bindings. At the same time ferocious barking and emptying of the bladder were observed. On the basis of special experiments — changing the time of the dog's confinement in the frame, eliminating certain irksome factors such as binding — and also by testing the dog outside of the frame (in the corridor) and by observing its behaviour in the company of other dogs, the author came to the conclusion that Melja was distinguished by a strongly manifested *reflex of slavery*, whose nature approached that of an unconditioned reflex. It is this peculiar reflex that is responsible for the extreme exaggeration of Melja's "formal behaviour" in the frame. During this period of immobility a process of accumulated inhibition develops in the central end of the cortical motor analyzer. But, in agreement with the law of *positive induction*, there is formed at the same point an accumulation of excitation which appears suddenly at the moment when the dog is freed. The strength of this "excitation-explosion" is proportional to the duration of the preceding period of standing in the frame (Frolov, 1925).

† Personal communication from P. S. Kupalov.

At this point the dog could no longer distinguish between them and its behaviour exhibited an abrupt change. It salivated profusely at the appearance of both circle and oval and attempted to escape from the frame. Further work in the laboratory proved impossible with this dog, but after a long vacation successful training was resumed. Again, however the animal became agitated when confronted by the task of distinguishing the circle from the almost circular oval.

Subsequently other instances of abnormal behaviour were encountered in which the conditioned salivary reflexes fluctuated in magnitude, diminished and finally disappeared. In some dogs chronic somnolence developed, but other animals exhibited various manifestations of immobility in the training frame such as holding food in the mouth without being able to chew and swallow it (Pavlov, 1941).

Further analysis disclosed, in these animals, a sequence of abnormal reactions to the conditioned stimuli. A phase of equalization in which conditioned responses of equal magnitude were elicited to stimuli both strong and weak was followed by a paradoxical phase in which the weak stimuli elicited larger responses than did the signals of greater intensity. Finally, during the ultra-paradoxical phase, only negative conditioned stimuli evoked the conditioned salivary reflexes (Pavlov, 1927).

Although Pavlov designated such abnormal states as experimental neuroses, he discovered that like conditions might result from traumatic experiences outside of the laboratory. For example, during a flood some of the dogs were threatened with drowning in the kennels. Following their rescue signs of neurosis were observed in deviations of well-established conditioned reflexes agreeing in detail with the abnormalities observed in the experimental neuroses produced under laboratory conditions (Pavlov, 1928).

In the discussion of the many cases of experimental neurosis observed in his laboratory Pavlov placed greatest emphasis upon the temperament of the dog, the characteristics of the conditioned stimuli, positive and negative, and upon the temporal relations of the stimuli. The training procedures which he found most effective in precipitating experimental neurosis included the development of progressively finer discriminations, of progressively longer delayed responses, and the sudden reversal of long familiar positive and negative conditioned stimuli.* Pav-

* For a useful summary of Pavlov's studies of the experimental neurosis see Babkin (1938).

lov failed, however, to give due consideration to the peculiarities of his training method, the employment of which led to the chronic disorders of behaviour which he so graphically described. That the habitual suppression of spontaneous activity by the animal standing in the conditioning frame might be an important etiological factor in the onset of the experimental neurosis was first suggested by observations of Liddell and Bayne(1927). A sheep in which motor conditioned reflexes were being established reacted to a sudden increase in the number of daily tests of a delayed conditioned response by an intractable, chronic agitation focused upon the reacting forelimb which now executed frequent tic-like movements. Furthermore, the animal persistently resisted attempts to lead it to the laboratory.

The nervous behaviour of this sheep strikingly resembled the abnormal reactions of Shenger-Krestovnikova's dog when its discrimination between oval and circle was disrupted. In the belief that the sheep had developed an experimental neurosis a systematic investigation of the circumstances suspected of contributing to its breakdown was undertaken. It happened that this sheep had for some years been employed in maze learning experiments and had never shown signs of nervousness or resistance to discipline even when confronted by a labyrinth from which it never learned to escape without errors. The difficult situation was met by procrastination and evasion with undisturbed calm. In fact, none of the many sheep and goats pushed to the limit of their maze learning ability ever showed extreme nervousness or other abnormalities of behaviour.

In the course of further studies by Liddell, James and Anderson(1934), Anderson and Liddell(1935), Anderson and Parmenter(1941) and Liddell(1942a) many cases of experimental neurosis in the sheep were observed over periods of 5 to 14 years. Their findings and the tentative conclusions which may be drawn therefrom are briefly as follows. The signs of experimental neurosis in the sheep substantially agree with those observed by Pavlov(1941) and Gantt(1943) in the dog and by Dworkin(1939) and Masserman(1943) in the cat. Experimentally neurotic behaviour in these mammals is stereotyped. It varies from somnolence, inertness and rigid immobility to hypersensitivity and overactivity, sometimes to the extreme of manic excitement. In the sheep an unpredictable waxing and waning of the agitated state is observed.

This is not the place in which to attempt a full account of the motor

and secretory manifestations of the experimental neurosis. Gantt(1943) says of the neurotic dog which he observed for many years: "If Nick had been a patient his symptoms would have been referred to as anxiety neurosis, merergasia, phobias, functional tachycardia, palpitation, asthmatic breathing, enuresis, ejaculatio praecox, gastric neurosis"(Gantt, 1943).

The frequency with which sheep subjected to long-continued training in the conditioned reflex laboratory develop experimental neurosis leads to the belief that the classical method of the conditioned reflex is something more than an impersonal observational procedure. Since, in the course of months or years of conditioning, a progressive change in the animal's behaviour occurs and that change approaches a pathological terminus — the experimental neurosis, it seems justifiable to characterize Pavlov's method as a traumatizing procedure. The animal's self-imposed restraint in the conditioning frame may lay the foundation for the later development of abnormal behaviour, but the operation of other factors is necessary for the appearance of the chronic disturbances of behaviour described above.

Liddell(1942a) suggests that the most significant feature of the conditioned reflex method for the production of disordered behaviour is its monotonous and unsatisfactory repetitiveness, as illustrated in the following experiment. A goat was conditioned according to an unvarying routine consisting of 10 conditioned signals(clicking of a telegraph sounder for 10 sec.), each signal being followed by a mild electric shock to the forelimb, with rest periods of exactly 2 min. between tests.* Repeated precise flexions of the limb in response to the clicking of the telegraph sounder soon gave place to a single deliberate flexion of the limb with a latent period of about 8 sec. The next phase involved stiffening of the forelimb at the signal and the raising of the stiffened limb by movement at the shoulder. When the animal was showing increasing difficulty in raising its rigid limb from the platform it was coming most willingly to the laboratory and exhibiting unusual quiet as it stood in the frame. It also paid the closest attention to faint noises from the experimenter's room. As difficulty in raising the foreleg increased this limb gave signs of enhanced sensitivity. First, a brief knock with the

* A slightly more complicated procedure is most often employed in our laboratory for the production of experimental neurosis. It consists of alternating positive and negative conditioned stimuli of equal duration, maintaining a constant interval between these stimuli.

side of the hand against the forefoot elicited a brief, precise flexion of the leg; but later, with the onset of the rigid, stiffening phase, a light touch of the finger on the forefoot was followed by an extremely rapid, small, tic-like movement.

This procedure for inducing the behavioural disorder described above has a twofold importance. It is the simplest means of precipitating a chronic disorder of behaviour and constitutes at present, therefore, the limiting case of neurosis-producing procedures. Secondly, it stresses the factor of timing in the production of nervous disorder.

CONCLUDING REMARKS

The accurate timing of neural events to the fraction of a millisecond is an enviable achievement of the present-day neurophysiologist. It may be that, through his interest in temporal measurement, his active co-operation can be secured in the task of interrelating data secured from the direct examination of functioning nervous tissue and data derived from the rapidly improving procedures for recording various physiological functions involved in conditioned reflex action.

Although the characteristics of the conditioned reflex and the manifestations of the experimental neurosis just described must be referred for eventual explanation to the operations of the central nervous system, the experimenter in the field of animal behaviour must derive his theoretical formulations from the data of interofective and exteroofective action. When it is possible, in the same animal, directly to examine the functioning of its nervous tissue and at the same time to record the changing patterns of effector action resulting from conditioning, a comprehensive theory to account for learned behaviour in terms of central nervous action and of effector action should be possible. Meanwhile, it is encouraging to see evidences that investigations in neurophysiology and in physiological psychology are ever more closely converging.

However, from the previous discussion it can be readily understood why investigations of the conditioned reflex and of the experimental neurosis have so infrequently been undertaken by physiologists. The physiologist cannot be concerned with an experimental animal as an individual. He cannot afford to invest months or years in exploring those idiosyncrasies of function which appear in the individual partly as the consequence of inheritance, but largely as the result of the slow changes

in the activities of the nervous system which accompany maturation, aging, and learning.

But this time-consuming exploration is a common procedure in clinical medicine and indispensable in psychiatric research. The medical importance of the conditioned reflex method is to be found in its fitness for the purpose of analyzing physiologically the intricate and often unstable patterns characteristic of the individual's behaviour. The method biases the investigator in favor of precise physiological detail in his observations of the complex bodily operations which for convenience are designated as psychical.

SUMMARY

In order to bring the investigation of the psychical secretion of saliva within the province of experimental physiology, Pavlov devised a training procedure for dogs which he designated as the conditioned reflex method. The essentials of the method are as follows: The dog with parotid fistula learns to stand on a platform where movement is restrained by a loose harness. Small quantities of food are supplied while the experimenter, from an adjoining room, can observe and record the salivary secretion and can present various stimuli, auditory, visual or cutaneous, which signal the forthcoming food. When food invariably follows the appropriate signal, when distractions are eliminated, and when the time between testing and the previous meal is kept constant, psychical secretion becomes fairly constant and predictable. Its uniformity suggests that of reflex action and, according to Pavlov, it differs from the ordinary reflex only in the greater number of conditions which must be satisfied to insure its predictability and in the fact that it is an individually acquired reaction. Psychical secretion, thus standardized, is designated as the conditioned reflex. Individually acquired reactions, whether secretory or motor, are classified as positive, negative, simultaneous, delayed, and trace conditioned reflexes.

Although Pavlov's theory of conditioned reflex action has not proved acceptable to the neurophysiologist, modifications and new applications of his technique have led to rapid advances in the physiological analysis of behaviour. The fact that physiological functions can be conditioned focuses attention upon the complex physiological integrations involved in the simplest habitual acts.

In motor conditioning to an electric shock applied to a limb the activities of single motor units during conditioning and extinction show changes of latency and rate of firing differing from the activities of these units during the elicitation and extinction of startle responses.

The cerebral cortex in mammals is not essential for simple conditioning and various afferent and efferent portions of the conditioned reflex arc are also dispensable. Sham rage aroused in the cat by electrical stimulation of the hypothalamus cannot be conditioned to such signals as a sound or a light.

In man conditioned motor reflexes such as the conditioned knee jerk more closely resemble voluntary movement of muscle than its reflex contraction. Even ordinarily involuntary reactions(*e.g.*, pupillary constriction to light and vasoconstriction to cold)can be brought under voluntary control by conditioning procedures and these conditioned reflexes in the human subject can be facilitated or inhibited by voluntarily induced sets.

In the conditioned reflex laboratory animals exhibit an unexpected degree of spontaneity, often giving conditioned reactions in the absence of appropriate stimuli. Moreover, their behaviour in the living quarters exhibits a quite "unreflex" influence of the previous specific laboratory conditioning.

Chronic states of disordered behaviour(experimental neuroses)are readily precipitated in animals subjected to conditioning by Pavlov's method. The animal's habitual restraint within the training frame, together with the monotonous and unsatisfying repetitiveness of the routine may be the principal strain-producing factors involved in this rigid conditioning procedure.

The investigator of conditioned reflex action, unlike the neurophysiologist, is primarily concerned with the experimental animal as an individual and is prepared to expend the time and effort necessary to explore in physiological detail the effects on its behaviour of maturation, aging and learning. His data must, however, be referred for eventual explanation to the operations of the central nervous system.

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The list originally included only those papers actually cited in the text; it embraces, however, the more important contributions to the experimental anatomy and physiology of the nervous system which have appeared since 1925. The bibliographical list of my previous book, *Muscular contraction* published in 1926 includes many pertinent references to earlier literature not given here. In citing journals the abbreviations are given in accordance with the conventions of the *World list of scientific periodicals*, 2nd ed., Oxford University Press, 1934. Citations in the text are made by date. Numbers in square brackets at the end of each entry indicate the pages of the present volume in which the article in question is cited. A number of recent references not cited in the text have been added after the book was in page proof. These entries are preceded by an asterisk and the relevant page of the present volume is also indicated in square brackets.

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INDEX OF SUBJECTS

A

- Ablations,
 - see also* Cerebral cortex, areas
 - areas 3-1-2, 359, 409
 - area 4, 382, 409
 - area 5, 359
 - motor effects, 414
 - area 6a (upper), 404 *et seq.*
 - area 6a β , 412
 - area 6b α , 412
 - area 6b β , 412
 - area 7, 357 *et seq.*
 - area 8, 412, 413
 - area 13, 420
 - area 17, 413, 414
 - area 19, 413
 - cerebellum, 470 *et seq.*
 - extrapyramidal system, 416
 - parietal, 357
 - taste, 367
- Acetylcholine, 67-78, 80
 - fright reaction, 218
 - liberation in blood, 218
- Action potentials,
 - areas 3-1-2, 355
 - asphyxia and pain, 25
 - caudate nucleus, 452
 - circulation and, 25
 - mixed nerve, 25
 - parietal lobes, 355
 - putamen, 497
 - thalamus, 354
- Acuity, visual, 323
- Aculalia, 366
- Adaptation, 11, 12, 14, 17
- Adiadochokinesis, 487
- Adiposogenital syndrome, 223, 243, 247
- Adjustor neuron, 1
- Adrenaline sensitization, 208, 209 *fn.*
- Adversive field, 397
- Afferents, stretch, 8
 - see also* Receptors
 - visceral, 26, 27, 225
- After-discharge, 96
 - and stretch reflex, 107
- After-potential, definition, 63
 - negative, 63
 - positive, 56, 63
- Agnosia, finger, 366
- Alexia, 334
- Allocortex, 274, 306, 446
 - cytoarchitecture, 297
- All-or-nothing principle, 13, 17
- Ammon's horn, 280, 300, 306, 312, 315
- Amygdala, 446
- Angular gyrus, 334
 - see also* Gyri
- Anodon, 81
- Anomia, 366
- Ansa lenticularis, 447, 448
- Ansiform lobe, 465, 467, 473
- Antipyretics, 236
- Anus, cortical area, 375
- Aphasia, 344
 - Broca's, 427
 - motor, 427
 - nominal, 366
 - semantic, 366
 - sensory, 366
 - syntactical, 366
 - verbal, 345, 366
 - Wernicke's, 366
- Aqueductus sylvii, 184, 186, 256
- Archipallium, 314
- Archistriatum, 446
- Architectonics, definition, 275
- Areas,
 - Broca's, olfactory, 304, 315
 - speech, 426
 - area 1, 356
 - areas 3-1-2,
 - ablation, 359
 - motor effects, 410
 - action potentials, 355
 - activation, 355
 - excitability, 395, 399

Areas (cont.)

areas 3-1-2 (cont.)

- sensation, 365
- spasticity, 410
- strychninization, 352

area 4,

- ablation, 382, 385
 - infants, 414
- activation of, 355
- atrophy, 385
- autonomic actions, 387, 433
- behaviour, 386, 422
- Berger rhythm, 373
- Betz cells, 373
- cerebellum and, 483
- chronaxie, 372
- dermatomes and, 375
- excitability, 371, 378, 401
- extinction, 379
- facilitation, 378, 379
- flaccidity, 383
- focal seizures, 375
- H-ion, 376, 377
- hopping, 357
- hyperventilation, 377
- infants, 373
- ipsilateral foci, 382
- laminar coagulation, 373
- memory, 385, 422
- movements, 382
- optimal stimuli, 372
- posture, 383
- reflexes, 384
- shivering, 387
- spasticity, 409
- strip region, 384
 - spasticity, 410
- strychninization, 352
- thalamocortical fibres, 358

area 5,

- ablation, 359
- excitability, 399
- sensation, 351, 365

area 6,

- ablation, infants, 414
- associated movements, 459
- autonomic actions, 433
- behaviour, 422
- bladder reflexes, 440
- caudate fibres, 497
- cerebellum, 483

chronaxie, 397

- excitability, 395, 401
- historical, 394
- inhibition from, 416
- ipsilateral area, 396
- memory, 422
- spasticity, 394
- strip region, 384
- strychninization, 352
- sweating, 435, 436
- thalamocortical fibres, 358
- volitional movements, 416
- area 6a (lower),
 - ablation, 412
- area 6a (upper),
 - ablation, 404
 - forced grasping, 407
 - intestinal motility, 438
 - ipsilateral control, 416
 - reflexes, 411
 - spasticity, 408, 409
- area 6a α (lower), excitability, 397
- area 6a α (upper),
 - excitability, 395, 396
 - movements, 396
- area 6a β , 396, 397
 - ablation, 412
 - adversive movements, 397
 - epilepsy, 397
 - forced grasping, 412
 - pyramid section, 431
 - strychninization, 354
- area 6b α , ablation, 412
- area 6b β ,
 - ablation, 397
 - excitability, 397
- area 7,
 - ablation, 360, 365
 - excitability, 399
 - sensation, 351, 365
- area 8,
 - ablation, 412
 - caudate fibres, 453
 - eyes, 398
 - lesions, parkinsonism, 413
 - nictitating membrane, 437
 - pupillary dilation, 437
- area 8a $\beta\delta$, excitability, 398
- area 8 γ , excitability, 399
- areas 9-12, 415
 - behaviour, 419, 422

Areas (cont.)

- areas 9-12 (cont.)
 - conditioned reflex, 424
 - delayed reaction test, 423
 - distractibility, 420
 - excitability, 435
 - historical, 418
 - localization, 426
 - memory, 422
 - neuroses, 424
 - problem box, 422
 - reflexes, 419
 - "sensory" change, 419
 - spasticity, 409
- area 13, 398, 420
- area 17, 325, 328, 329
 - ablation, 413, 414
 - eye movements, 399
- area 18, 333
 - hallucinations, 399
 - tumours, 334
- area 19, 333, 343, 351
 - ablation, 413
 - pupillary constriction, 437
- area 22, excitability, 399
- areas 41-42,
 - cytoarchitecture, 276, 305
- areas 45-46, 426
- cortical,
 - see also* Cerebral cortex, areas
 - audition and, 340
 - face, strychninization, 352
 - gigantopyramidal, *see* area 4
 - ipsilateral, 380
 - area 6 and, 396
 - occipital, 306
 - parolfactory, 431
 - postcentral, motor response, 399
 - prefrontal, definition, 419
 - premotor, 394
 - preoccipital, 306
 - sensory, encephalization, 358
 - strip, 409
 - tail, 372
- Argyll Robertson pupil, 180, 184, 188
- Arnold's bundle, 310
- Arrhythmia, cardiac, 231
- Arteries,
 - perforating, 266
 - thalamogeniculate, 266
- Arthritis, 102

- atrophy, 101
 - reflexes in, 101
- Associated movements, 458
 - area 6, 460
- Astacus*, 81
- Asynergia, 487
- Ataxia,
 - dorsal root, 149
 - locomotor, 149, 154
 - trunk, 475, 481, 483, 488
- Athetosis, 454, 460
 - surgical relief, 457
- Atrophy, 385
 - muscular, 101
- Attitudinal reflexes, 167
- Audition, acuity, 343
 - central deafness, 341
 - cochlea and, 337, 338
 - cortical area, 339
 - history, 337
 - koniocortex, 338
 - projections, 337, 338
- Auditory projection, 259
- Autogenous inhibitors, 152
- Autonomic epilepsy, 249
- Autonomic system, 223 *et seq.*
 - afferents, 205
 - area 4, 387
 - cortex and, 429 *et seq.*
 - definition, 193
 - efferents, 225
 - functional levels, 441, 442, 443
 - functional regulation, 214
 - gastric motility, 214
 - gastrointestinal regulation, 214
 - generative function, 215
 - history, 189
 - homeostasis, 191, 192
 - peptic ulcer, 241
 - pyramids and, 389
 - sex and, 215
 - somatic overlap, 442
- Axon hillock, 40

B

- Babinski's sign, 101, 132, 134, 223, 247
- Baillarger's bands, 274
- Basal ganglia,
 - associated movements, 458
 - autonomic effects, 451
 - chorea, 456

- Basal ganglia (cont.)
 - clinical physiology, 454
 - connections, 446
 - excitability, 445, 449
 - historical, 445
 - lesions, 450
 - nuclei, 447
 - pathology, 458
 - rigidity, 457
 - schema, 447
 - stimulation, 449
 - strychninization, 452
 - tremor, 457
 - Basis pedunculi, 448
 - Bear, motor area of, 139
 - Behaviour,
 - area 4, 386, 422
 - area 6, 422
 - areas 9-12, 422
 - Berger rhythm, 373, 378
 - area 4, 373
 - H-ion, 377
 - laminar coagulation, 373
 - Betz cells, 276, 302, 307, 308, 313
 - area 4, 307
 - discovery, 274
 - Bladder, 231
 - reflexes of, 99, 126, 127, 128, 440
 - spastic, stretch reflex, 441
 - spinal man, 128, 129, 133
 - Blindness, psychic, 343
 - Blood pressure,
 - cortex and, 431
 - medullar level, 442
 - regulation, 241
 - spinal level, 442
 - Body, geniculate, medial, 339
 - image, 366
 - trapezoid, 339
 - Boutons terminaux*, 53
 - cerebral cortex, 56
 - degeneration, 55
 - autonomic, 443
 - distribution, 53
 - dorsal roots, 21
 - fixation, 55
 - methods of staining, 55
 - origin of term, 53
 - sympathetic, 56
 - Brachium conjunctivum, 467
 - pontis, 467
 - Bradyopus*, 20
 - Broca's area, olfactory, 304, 315
 - speech, 426
 - Brown-Séquard syndrome, 135, 142
 - Bulimia, 420, 438, 439
 - Bundle, Arnold's, 310
 - posterior longitudinal, 57
- C
- Cajal cells, 275
 - Caloric stimulation, 344
 - Capsula interna, 256
 - Capsule, Tenon's, 202
 - Carbohydrate metabolism, hypothalamus, 238
 - Cardiovascular system, cortex and, 430
 - Caudate nucleus,
 - action potentials, 452
 - anatomy, 446
 - athetosis, 454
 - chorea, 456
 - connections, 447
 - cortical fibres, 310, 311, 452
 - excitability, 449, 450
 - lesions, 450, 451
 - Cells,
 - amacrine, 322
 - Betz, 276, 302, 307, 308, 313
 - area 4, 307
 - discovery, 274
 - Cajal, 275
 - dorsal horn, 24
 - ganglion, 70
 - Golgi, 274, 289
 - Meissner's, 4
 - Merkel, 3, 4
 - Purkinje, 469
 - Schwann, 40
 - Central excitatory state, 121
 - definition, 59
 - Central inhibition,
 - see* Inhibition
 - Cerebellar seizure, 98, 155
 - Cerebellum,
 - ablation, 470, 471
 - adiadochokinesis, 487
 - afferents, 465, 466
 - anatomy, 465
 - ansiform lobe, 473
 - anterior lobe, 181, 466, 467, 476, 484

Cerebellum (cont.)

- area 4 and, 482
- area 6 and, 483
- asynnergia, 487
- atrophy, 481
- cerebral interaction, 479, 481, 482
- comparative anatomy, 464 *et seq.*
- compensation, 472
- decerebrate rigidity, 472
- dentate nucleus, 469
- dominance, 489
- dysmetria, 485
- efferents, 468
- emboliform nucleus, 469
- eye movements, 487
- flocculonodulus, 464, 467, 470, 475
- functions, 475
 - pyramis, 476
 - uvula, 476
 - vestibular, 475
- gait, 463
- globose nucleus, 469
- historical, 463
- hypotonia, 471, 484
- incoördination, 487
- localization, 473, 488
- Luciani triad, 472
- motor weakness, 486
- movement disorders, 485
- nuclei, 469 *et seq.*
 - destruction, 480
- nystagmus, 487
- paraflocculus, 467
- paramedian lobe, 473
- peduncles, 466
 - inferior, 481
 - middle, 481
 - section of, 480
 - superior, 480
- posterior lobe, 465
- pyramis, 467
- sensory effects, 487
- speech, 463, 484, 489
- stimulation of, 181
- stretch reflexes and, 476
- symptomatology, 470
- terminology, 470
- tremor, 471, 482, 486
- trunk ataxia, 488
- uvula, 467
- weakness, 486

Cerebral cortex,

- action potentials, 381
- afferents, 281, 286, 287
- areas, all types, 281
 - area 1, 353
 - area 2, projections, 307
 - areas 3-1-2, 410
 - ablation, 359
 - motor effects, 411
 - action potentials, 355
 - activation, 355
 - cytoarchitecture, 276, 297, 304
 - excitability, 395, 399
 - facilitation, 379
 - sensation, 365
 - strychninization, 352
- area 4, 370
 - ablation, 382, 385
 - activation, 355
 - atrophy, muscular and, 385
 - autonomic actions, 387, 433
 - behavioural changes, 386, 422
 - Berger rhythm, 373
 - Betz cells, 373
 - boundaries, 302
 - cerebellum and, 481, 483
 - chronaxie, 372
 - cytoarchitecture, 276
 - dermatomes and, 375
 - excitability, 371, 378, 401
 - extinction, 379
 - extrapyramidal fibres, 310
 - facilitation, 378, 379
 - flaccidity, 383
 - focal seizures, 375
 - foci, 370
 - granules of, 297
 - H-ion, 377
 - hopping, 357
 - hyperventilation, 377
 - infants, 373, 414
 - ipsilateral foci, 382
 - laminar coagulation, 373
 - map, 303
 - memory and, 385, 422
 - movements, 382
 - optimal stimuli, 372
 - pH of, 378
 - placing, 357
 - posture, 383
 - pyramid section and, 388, 401

- Cerebral cortex, areas (cont.)
- area 4 (cont.)
 - reflexes, 384, 412
 - shivering, 387
 - somatic sensation, 386
 - spasticity, 384, 409
 - stratification of, 297
 - strip,
 - spasticity, 384, 410
 - strychninization, 352
 - subdivisions, 302
 - thalamocortical fibres, 255 *et seq.*, 358
 - area 5,
 - ablation, 359
 - cytoarchitecture, 285, 304
 - excitability, 399
 - motor effects, ablation, 414
 - projections, 306
 - sensation, 351, 365
 - area 6,
 - ablation, infants, 414
 - associated movements, 459
 - behavioural changes, 422
 - bladder reflexes, 440
 - boundaries, 302
 - caudate fibres, 453
 - cerebellum and, 483
 - chronaxie, 397
 - cytoarchitecture, 304
 - excitability, 395
 - forced grasping, 394
 - historical, 394
 - ipsilateral area, 396
 - memory and, 422
 - pyramid section, 401
 - sensation and, 394
 - spasticity, 394
 - strip region, 384
 - strychninization, 352
 - subdivisions, 304
 - sweating, 435, 436
 - thalamocortical fibres, 358
 - vasodilation, 433
 - area 6a (lower), 412
 - excitability, 397
 - area 6a (upper), 354, 396
 - ablation, 404, 412
 - adversive movements, 397
 - epilepsy from, 397
 - forced grasping, 405, 407, 412
 - grasp reflex, 405
 - groping, 405
 - intestinal motility, 438
 - ipsilateral control, 416
 - movement changes, 404
 - pyramid section, 396
 - reflexes, 411
 - righting, 406
 - spasticity, 408, 409
 - area 6a α (upper), 395, 396
 - excitability, 396
 - movements, 396
 - area 6b α , ablation, 412
 - area 6b β ,
 - ablation, 412
 - excitability, 397
 - area 7,
 - ablation, 360, 365
 - cytoarchitecture, 305
 - excitability, 399
 - sensation, 351, 365
 - area 8,
 - ablation, 412
 - caudate fibres, 453
 - eyes, 398
 - nictitating membrane, 437
 - parkinsonism, 413
 - pupillary dilation, 437
 - area 8a $\beta\delta$ excitability, 398
 - area 8 γ , excitability, 399
 - areas 9-12, 415
 - behaviour, 442
 - conditioned reflex, 424
 - cytoarchitecture, 304
 - delayed reaction test, 423
 - excitability, 399
 - historical, 418
 - localization, 426
 - memory, 422
 - neuroses, 424
 - problem box, 422
 - recall, 422
 - reflexes, 419
 - sensory change, 419
 - spasticity, 410
 - area 13, 398, 420
 - area 17, 280, 285, 306, 321, 325
 - ablation, 413, 414
 - cytoarchitecture, 277
 - eye movements, 399
 - area 18, 306, 333

Cerebral cortex, areas (cont.)

- area 18 (cont.)
 - hallucinations, 399
 - tumours, 334
- area 19, 280, 306, 333, 343, 351
 - ablation, 413
 - eye movements, 399
 - pupillary constriction, 437
- area 22, 399
- area 28, 280, 296
 - cytoarchitecture, 277
- areas 41-42,
 - cytoarchitecture, 276, 305
- areas 45-46, 304, 314, 426
- association fibres, 286, 287
- autonomic function, 430
 - historical, 429
- autonomic pathways, 443
- behaviour change, 419
- Brodmann's areas, *see* Areas
- cardiovascular, 432
- cell types, 281
- cerebellar interaction, 482
- corpora quadrigemina, 279
- corticospinal projections, 307
- distractibility, 420
- effector layers, 290
- electrocorticogram, 318, 402 *et seq.*
- embryology, 275, 278
- gastro-intestinal effects, 437
- general organization, 279
- heart-rate, 432
- heat regulation, 433
- intracortical neuron chains, 293
- intussusception, 438
- ipsilateral, 381
- lacrimation, 440
- laminae, 283
- layers, 283
- micturition, 440
- neuron interaction, 290
- Nissl stain of, 299
- pain and, 351
- pilomotor effects, 436
- placing reactions, 176
- pupillary dilation, 440
- receptive layers, 290
- respiration, 441
- righting reflexes, 175
- salivation, 440
- short axon neurons, 289

- stomach and, 438
- stratification of, 279, 283
- strip region, 302
- strychninization, 351
- sympathetic action, 432
 - vasoconstrictor, 433
- Cerebral dominance, 344
- Cervical sympathetic,
 - see* Sympathetic
- Chaddock's sign, 385
- Chalasis, 415
- Chemical mediators, 67, 217
- Chiasm, optic, 323
- Choline esterase, 69, *et seq.*, 217
- Chorea, 454, 460
- Chromatolysis, 27, 38, 39, 252
- Chromidial substance, 38
- Chronaxie,
 - area 4 and, 372
 - area 6 and, 397
 - corticospinal tract, 372
- Clarke's column, 23
- Clasp-knife effect, 408, 457
- Clastrum, 446
- Clonus, 135
- Cochlea, 340
 - ablation, 342
 - primary neurons, 337
- Cog-wheel effect, 457
- Colic, renal, 100
- Colliculi,
 - anterior, 181
 - pilomotor reactions, 436
 - function of, 184
 - inferior, 339
- Column, Clarke's, 23
 - Stilling's, 23
- Commissure,
 - anterior, 226
 - posterior, 181, 184
- Conditioned reflexes, 357, 424, 439
 - proprioceptive, 386
 - Sherrington's discovery, 131
- Conduction, antidromic, 28
- Cones, 322
- Constriction, pupillary, 437
- Contraction, postural,
 - unit discharge in, 46, 47
- Convergence, 186
 - principle of, 22, 37, 96
- Convulsions, 376, 378

- Cordotomy, 24
 Corpora quadrigemina, light reflex, 181
 stimulation, 181
 Corpus callosum, 315
 grasp reflex, 406
 Corpus cerebelli, 465
 Corpus subthalamicum, 256
 Corpuscles,
 Golgi-Mazzoni, 3, 5
 Grandy's, 4
 Meissner's, 3-6, 17
 Merkel's, 3-5, 17
 Pacinian, 5, 8, 9, 10, 17, 23, 24, 26
 Ruffini, 2, 4, 5, 6, 17
 sensory, 4
 tactile, 4
 Cortex, cerebral,
 see Cerebral cortex
 Cortical relay nuclei,
 see Nuclei, thalamic
 Corticospinal tract, 305
 Corticothalamic projections, 264, 354
 functions, 268, 271
 Craniosacral,
 see Parasympathetic
 Culmen, 465, 466, 468
 Curare, 429
 Cyst, suprasellar, 155, 156
 Cytoarchitectonics, 275
 Cytoarchitectural areas,
 see Cerebral cortex
 maps, 299
 Cytoarchitecture, history, 274 *et seq.*
- D
- Darkschewitschi's nucleus, 448
De usu partium, 252
 Deafness, central, 342, 345
 Decerebellate-thalamic dog, 482
 Decerebrate rigidity, 143 *et seq.*, 164
 anatomy, 146
 anesthesia, 144
 dog, 144, 171
 dorsal roots, 147
 VIIIth nerve, 147
 guinea pig, 144
 hemiplegia, 147
 history, 143, 144
 hypothalamus and, 145
 inhibition of, 148
 labyrinth, 145, 156
 man, 147, 155, 156, 157
 monkey, 171
 muscle receptors, 149
 peripheral nerve and, 148
 primates, 144
 proprioceptive system, 148
 pyramidal tract, 144
 rabbit, 144
 red nucleus, 145
 tonic neck reflexes, 155
 vestibular nuclei, 145, 146
 Declive, 465
 Decorticate rigidity, 171, 172
 Decussation, Forel's, 448
 Defecation, reflex, 129, 134
 spinal man, 130
 stimulus for, 130
 Deficiency phenomena, cerebellar, 472
 Degeneration, *boutons*, 443
 Marchi, 307
 nerve, 40
 retrograde, 39, 252, 325
 transneuronal, 38, 325
 Wallerian, 40
 Deiter's nucleus, 157
 Delayed reaction test, 423
 Dentate nuclei, 469
 lesions, 480
 Dermatomes, 30, 36
 antidromic action of, 31
 determination of, 31
 man, 30, 33
 monkey, 30
 parietal lobes, 355
 pilomotor, 30
 sudomotor, 30
 vasoconstrictor, 30
 Detonator action, 61
 Diabetes insipidus, 223, 232, 233, 234,
 246
 Diabetes mellitus, 239
 origin of term, 246
 Dilation, pupillary, 437, 440
 Diplegia, cortical, 440
 Discrimination of roughness, 358, 359, 360
 of weight, 358, 359, 360
 man, 364
 Diseases,
 disseminated sclerosis, 487

Diseases (cont.)

- Hirschsprung's, 215
- lenticular degeneration, 445
- Pick's, 440
- Raynaud's, 208
- schizophrenia, 440
- Distractibility,
 - areas 9-12, 420
- Dominance, left hemisphere, 344
- Dorsal roots, decerebrate rigidity and, 147
- Doubled-up posture, 98, 99
- Dreamy states, 346
- Dura mater, 97
- Dysmetria, 471
 - cerebellar, 485

E

- Effectors, independent, 1
- Ejaculation reflex, 125
- Electroencephalograms, 248, 454
- Emboliform nuclei, 469, 480
- Emotion,
 - parasympathetic and, 219
 - theory of, 131
- Encephalitic lethargica, 244
- Encephalization, 361
 - sensory areas, 358
 - vision, 331
- End bulbs, Krause's, 3, 4, 5, 17
- End feet, 53
- End organs,
 - rate of discharge, 13
- Endfüsse*, 53
- Ending,
 - annulospiral, 8, 15
 - flower spray, 8, 15
 - free nerve, 10
 - hair root, 4
 - pain, 16
 - pressure, 9
 - tactile, 4, 16
 - tendon, 17
 - tension, 8
- Endkolben*, 53
- Epilepsy,
 - area 6a β , 397
 - cortical,
 - autonomic disturbances, 429
 - focal, 369, 375

- ipsilateral, 380
 - sweating in, 435
- gastric aura, 439
- respiration and, 398
- Equilibrium, 475, 483
- Erosions, gastric, 439
- Erythrocebus*, 137
- Eserine, 68 *et seq.*
- Euphoria, 425
 - frontal lesion, 420
- Excitability,
 - areas 3-12, 395, 399
 - area 4, 371, 378, 401
 - area 5, 399
 - area 6, 395, 401
 - area 6a α (lower), 397
 - area 6a α (upper), 396
 - area 6b β , 397
 - area 7, 399
 - area 8a β δ , 398
 - area 8 γ , 399
 - areas 9-12, 399
 - area 13, 398, 420
 - area 22, 399
 - basal ganglia, 445, 449
 - caudate nucleus, 449
 - corticospinal tract, 391
 - extrapyramidal system, 416
 - pyriform lobe, 317, 449
 - tuberculum olfactorium, 317
- Excitatory process, local, 66
- Exophthalmos, 29, 202
- Experimental neuroses, 424, 425
- Exteroceptors, 17
- Extinction, 377
- Extrapyramidal system,
 - see also* Basal ganglia
 - excitability, 416
 - functional levels, 458, 459
 - general functions, 400, 459, 460
 - ipsilateral control, 415
 - release phenomena, 459
 - volitional movement, 414
- Eyes,
 - see also* Horner's syndrome
 - convergence of, 186
 - cortical fields, 398, 413
 - area 8, 398
 - ablation, 412
 - movement, 398

Eyes, cortical fields (cont.)
 area 8 (cont.)
 pupils, 398
 area 17, ablation, 413
 area 19, movements, 399
 cytoarchitecture, 304
 pupils, 413
 pupillary dilation, 437
 iris, 203
 light reflex, 186
 movements of, 181, 187
 area 17, 399
 cerebellar, 487
 muscles, 186, 201, 202
 myosis, 202
 optic chiasm, 258
 orbit, 201
 ptosis, 202
 retina, 258
 vasomotor fibres, 203

F

Face area, strychninization, 352
 Facilitation, 56, 65, 138, 378, 379
 areas 3-1-2, 379
 Fanning sign, 412
 Fasciculi, post longitudinal, 338
 Fastigial nuclei, 469
 lesions, 428
 Fat metabolism, 238
 Fibres,
 afferent, 286, 287
 association, 284, 287
 efferent, 28
 extrapyramidal, 309
 intrafusal, 8, 14
 postganglionic, 68
 eye, 201
 heart, 204, 205
 lower limbs, 207, 209
 upper limbs, 209
 preganglionic, heart, 204
 lower limbs, 209
 origin, 198
 pyramidal, 308
 thalamocortical, 358
 unmyelinated, 19, 25
 Final common path, 37, 96, 119, 141
 Finger agnosia, 366

Fissura, calcarina externa, 261
 posterolateralis, 464, 466
 prima, 465
 sylvii, 305, 338
 Flaccidity, cortical, 383
 pyramidal, 388
 Flexion, monoplegic, 100
 paraplegic, 136
 reflex, definition, 52
 Flocculonodulus, 488
 anatomy, 464
 connections, 467
 functions, 475
 syndrome, 483
 Flocculus, 466, 473
 Forced circling, 413
 grasping, 405
 area 6a (upper), 407
 area 6a β , 412
 discovery, 394, 404
 Forel's decussation, 448
 Fovea centralis, 323
 Fröhlich's syndrome, 223, 247
 Frontal association areas,
 see also Cerebral cortex, areas 9-12
 lobotomy, 425
 Function, vestibular, 343
 Fundamental experiment, 51

G

Ganglia,
 basal,
 associated movements, 458
 athetosis, 454
 chorea, 454
 clinical physiology, 454
 connections, 446
 excitability, 445, 449
 historical, 445
 lesions, 450
 nuclei, 447
 pathology, 457
 rigidity, 457
 stimulation, 449
 tremor, 457
 ciliary, 186
 coeliac, 99
 inferior cervical, 207
 lumbar, 207

Ganglia (cont.)
 Scarpa's, 337
 stellate, 207, 432
 superior cervical, 195, 207
 superior mesenteric, 99
 Gastric erosions, 439
 juice, psychic flow, 439
 Gastrocnemius, lateral, 58
 medial, 58
 Gastro-intestinal effects, cortical, 437
 functions, 214
 Geniculate bodies, 325
 lateral, 38, 258, 325, 326, 328
 light reflex, 184, 185
 medial, 259, 338, 339
 Geniculocalcarine tract, 327
 Gennari's line, 274, 306
 Glands,
 salivary, 210
 sex, 240
 suprarenal, 240
 sweat, 211
 innervation, 211
 Globose nuclei, 469
 lesion, 480
 Globus pallidus, 254, 256, 446, 447
 lesions, 451
 Golgi apparatus, 38, 39
 cells, 274, 289
 method, 278, 283
 tendon organs, 152
 Gonda's sign, 101, 412
 Gordon's sign, 385
 Granules, Nissl, 38
 Grasp reflex, 168, 405, 406, 407, 408
 sweating and, 443
 Grooming habit, 405
 Groping, 405, 406
 area 6a (upper), 405
 Gudden's atrophy, 252
 Gyri, angular, 261, 305, 321, 334
 callosal, 315
 cerebral, 261
 cingular, 318, 348
 dentate, 316
 fasciolar, 315
 Heschl's, 337, 339, 340
 hippocampal, 316, 348
 intralimbic, 315
 rhinencephalic, 314

 sigmoideus, 421
 supramarginal, 261, 305, 321, 334
 uncinate, 315

H

Habenula, 256
 Hallucinations,
 auditory, 340, 345, 351, 399
 paresthetic, 345
 smell, 337
 tactile, 351, 352
 taste, 337
 thermal, 351
 vestibular, 399
 visual, 334, 346, 398, 399
 Handedness, 344
 Head turning, 413
 Heart, innervation of, 204
 Heat loss, 235
 production, 236
 regulation, 234, 244
 antipyretics, 236
 blood temperature and, 236
 cortex and, 433
 Hemianopsia, homonymous, 321
 binasal, 323
 bitemporal, 323
 Hemiballismus, 458
 Hemidecortication, 265, 270
 effects of thalamus, 265
 sensory effects, 265
 Hemiplegia, autonomic changes, 433
 decerebrate rigidity, 147
 pilomotor changes, 436
 Hemoglobin, muscle, 109
 Heschl's gyrus, 337, 339, 340
 H-ion concentration, cortex, 378
 Hippocampus, 315, 316
 Hippus, 413
 Hirschsprung's disease, 215
 Hoffmann's sign, 411, 412
 Homeostasis, 191
 Hook bundle, 467
 Hopping reactions, 177
 Horner's syndrome, 180, 202, 203
 Horsley-Clarke technique, 231, 266
 Hunger, morbid, 420, 438, 439
 Hyperreflexia, 118
 Hyperesthesia, thalamic, 267

Hyperkinetic states, 420, 456
 Hypersomnia, 247, 248
 Hyperthyroidism, 202
 Hypometria, 471, 479
 Hypothalamus, 223 *et seq.*
 adiposogenital syndrome, 238, 247
 anatomy, 224
 autonomic epilepsy, 249
 blood pressure, 240, 241
 supply, 229
 carbohydrate metabolism, 238, 239
 cardiac regulation, 242
 decerebrate rigidity and, 145
 diabetes insipidus, 223, 232, 246
 eye, 242
 fat metabolism, 238
 functions of, 241, 243, 244, 250, 253
 gastric functions, 240, 241
 heart and, 231
 heat regulation, 234
 history, 223
 hypersomnia, 224, 247, 248
 hyperthermia, 247
 intestinal motility, 439
 parasympathetic centres, 231, 249
 pituitary, 223
 sex, 240
 sleep, 220, 240
 stimulation of, 231
 sympathetic centres in, 230
 syndromes of, 246, 249
 Hypotonia, 471
 cerebellar, 479, 484

I

Incontinence, cortical, 440
 Incoördination, cerebellar, 483
 Infants, area 4, 373
 ablation, 414
 area 6,
 ablation, 414
 cortical responses, 373
 grasp reflex, 408
 myelinization, 373
 Inhibition, 86
 after potentials and, 86, 378
 autogenous, 152
 central, 81

 cortical, 378, 388, 401
 history, 81
 humoral theory, 85
 knee jerk, 82
 peristalsis, 81
 spinal shock and, 138
 subnormal period, 86
 theories, 85
 Wedensky, 85, 86
 Inhibitory process, central, 84
 Innervation ratios, 42
 reciprocal, 99, 101, 102, 114, 115, 116,
 119
 tonic, 404
 Insulin, liberation, 212
 Integration, definition, 140, 141
 Interface, polarized, 66
 Intermediate grey, 23
 Internuncial, potentials of, 64
 Interoceptor, 2, 17
 Interpositus nucleus, 469
 Intestinal motility, cortex and, 437
 Intraventricular injections, 249
 Intussusception, 438
 Ipsilateral area, 380, 381, 382
 control, 415
 Iris, 203
 Isicortex, 274
 Isolated movements, 382

J

Jacksonian cerebellar seizures, 155
 focal seizures, 375
 see also Epilepsy, focal

K

Kernig's sign, 98, 102
 Kinesthesia, 364
 Knee jerk, 89
 decerebrate, 83
 inhibition, 82, 83, 138
 spinal, 83, 138
 Knobs, *see* Boutons
 Koniocortex, 259, 338
 Körperstellung, 163

L

Labyrinth, ablation, 172
 anatomy, 169
 decerebrate rigidity, 147
 grasp reflex, 408
 Labyrinthine reflexes, 169
 red muscle, 111
 Lacrimation, 440
 Laminar coagulation, 373
 Larynx, cortical field, 397
 Latency, reflex, 56
 Lateral geniculate bodies, *see* Geniculate
 Laughing, reflex, 182
 Law, Magendie, 18
 Lemnisci, lateral, 339
 Lengthening reaction, 150, 151, 408
 inhibition and, 152
 nature, 152
 Lenticular nuclei, 446
 Lesions,
 basal ganglia, 450
 caudate nucleus, 451
 dentate nuclei, 480
 emboliform nuclei, 480
 fastigial nuclei, 480
 frontal,
 euphoria and, 420
 globose nuclei, 480
 globus pallidus, 451
 putamen, 451
 strip, 309
 supraoptic nuclei, 225
 tuber, 225
 Leucotome, 425
 Light discrimination, 332
 Lingula, 478
 Lobe, ambiens, 315
 ansiform, 465, 473
 anterior cerebellum, 484
 cerebral, 259
 flocculonodular, 464
 frontal, 418 *et seq.*
 boundaries, 301
 cytoarchitecture, 298
 granules, 298
 limbic, 315
 occipital, 305, 321
 ablation, 329, 330
 paramedian, 465, 473

 parietal, 304, 305, 348 *et seq.*
 ablation, 357, 359 *et seq.*
 action potentials, 355
 localization in, 355
 organization, 355
 stimulation, 350
 pyriform, 277, 314
 excitability, 317
 functions, 317
 semilunaris, 315
 temporal, 259, 300, 315, 337 *et seq.*
 ablation, 344
 audition, 345
 cytoarchitecture, 305
 speech, 346
 tumours, 337, 346
 vision, 337
 Lobotomy, frontal, 425
 Local static reaction, 164
 Localization, areas 9-12, 426
 Locomotor ataxia, 149, 154
 Long circuiting, 97
 Loop, Meyer-Archambault, 327
 Luciani triad, 471, 472
 Luys' body, 446, 448

M

Macula, 323, 326
 cortical projection, 327, 329, 330
 sparing, 329, 330
Maculae sacculi, 173
 Magnet reaction, 165
 Magnus and de Kleyn reflexes, 155, 156
 history, 163
 Mammillary bodies, 145, 226
 Marchi degeneration, 307
 Medulla oblongata, 143, 157
 blood pressure, 442
 cardiovascular control, 161
 deglutition, 157
 respiration, 158, 159, 160, 161
 sweating, 442
 vasomotor reflexes, 161
 vomiting, 157
 Medullary pyramids, *see* Tracts
 Medulloblastoma, 484
 Megacolon, 215
 Membrane, nictitating, 437

- Memory, area 4 and, 386, 422
 area 6 and, 422
 areas 9-12, 422
 cortical lesion, 422
 recent, 427
 remote, 427
 Mendel-Bechterew sign, 411, 412
 Meningitis, 102, 186
 reflexes in, 97
 Mesencephalon, 181
 Metencephalon, 180
 Method, Golgi, 278
 Nissl, 278
 Meyer-Archambault loop, 327
 Meyer's loop, 327
 Micturition, 126, 440
 Midbrain, 183
 animal, 146
 lesion of, 183
 Mitochondria, 38
 Monkey, spider, 20, 372, 473
 Monoplegic flexion, 101
 Morbid hunger, 420, 438, 439
 Motor aphasia, 426
 area, *see also* Cerebral cortex, area 4
 bear, 139
 deafferentation, 149
 response, postcentral area, 351
 unit, 37, 38
 action potentials, 45
 bifurcation, 43
 definition, 37, 41
 functional activity, 44
 innervation ratio, 37, 42
 muscle fibre, white, 42, 43
 rate of discharge, 44
 reflex tension, 47
 stretch and, 44
 tension, 41, 47
 Movements, associated, 458
 area 6, 460
 disorders, cerebellar, 485
 Muscle spindle, 8
 Muscles, antigravity, 46
 atrophy, 101
 crureus, 42
 deafferentation, 149
 dilator pupillae, 201
 end organs, 13
 extensor longus digitorum, 42, 44
 extraocular, 57
 gastrocnemius, 42, 43, 110
 hemoglobin of, 109
 innervation, 7
 Müller's orbital, 201, 202
 receptors,
 decerebrate rigidity, 149
 red, 43, 81, 110, 111
 posture, 107, 108
 semitendinosus, 42, 95
 soleus, 42, 44, 45, 110
 tenuissimus, 41, 43
 tibialis anticus, 92
 vasomotor innervation, 9
 white, 43
 Myelencephalon, 180
 Myelinization, infants, 373
 Myeloarchitectonics, 275
 Myographs, 92
 Myosis, 180
- N
- Neck reflex,
 see also Postural reflexes
 red muscle, 111, 112
 Neocerebellum, 465, 467
 functions, 478
 hypotonia, 479
 Neopallium, 274
 Nerve endings, free, 2
 energies, specific, 6
 nets, 2
 Nerves,
 anterior tibial, 95
 Ist, 214, 215
 IIInd, 226
 IIIrd, 57, 180, 181, 184, 186, 198
 IVth, 181
 Vth, 180, 187
 VIIth, 180, 181, 187
 VIIIth, 163, 338, 344, 487
 IXth, 198
 Xth, 198
 inhibitory, 81
 intercostal, 189
 internal saphenous, 95
 obturator, 95
 peripheral, decerebrate rigidity and, 148
 pilomotor, 210

- Nerves (cont.)
 popliteal, 95
 quadriceps external, 95
 sciatic, 95
 splanchnic, 209
 section of, 99
- Neurofibrils, 38
 conduction by, 38
 functions of, 38
 living, 39
- Neuron, characteristics, 37
 cochlea, 337
 definition, 37
 doctrine, 52
 excitability cycle, 63
 internuncial, 60, 85
 circus excitation, 61
 intracortical, 293
 origin of term, 52
 permeability of, 66
 rotational activation, 67
 short axon, 289
- Neuroses, experimental, 424, 425
- Nicotine, synaptic action, 27
- Nictitating membrane, 223, 437
- Nissl method, 278
 stain, cerebral cortex, 299
 substance, 39
- Nociceptive response, 91, 101
- Nociceptor, 3
- Nocifensor system, 28
- Nodulus, 465, 466, 475
 tumours, 484
- Nuclei, abducens, 448
 amygdala, 446
 anterior, 255
 anteroventralis, 256, 261
 Bechterew, 157
 Burdach, 24
 caudatus, 256
 action potentials, 450
 anatomy, 446
 athetosis, 454
 behaviour, 419
 chorea, 455
 connections, 446, 453
 cortical fibres, 447, 453
 excitability, 499 *et seq.*
 lesions, 451
 centralis lateralis, 261
 centralis medialis, 254
 centrum medianum, 252, 254, 256, 447
 cerebellar, 480
 claustrum, 446
 cochlearis, 259, 338, 339
 corpus Luysii, 446, 447, 448, 458
 corpus quadrigeminum, 181
 superior, 413
 cranial, 111rd nerve, 57, 183, 184, 188
 cuneate, 24, 257
 Darkschewitschi, 448
 Deiters, 157
 dentatus, 469, 480
 Edinger-Westphal, 184, 188
 emboliformis, 469, 480
 face, 448
 fastigius, 466, 469, 480
 flocculonodulus, 470
 Forel, 448
 geniculatus, 259
 lateralis, 256
 medialis, 256
 globosus, 469, 480
 globus pallidus, 446, 447
 Goll, 24
 gracilis, 24, 257
 grisea centralis, 254
 habenular, 261
 hypoglossal, 448
 hypothalamic, 225, 443
 dorsomedialis, 225, 226
 posterior, 225, 226, 227
 ventromedialis, 225, 226
 intercalatus, 226
 interpositus, 469
 interstitial, 448
 intralaminar, 254
 lateralis posterior, 256
 lenticular, 446
 limitans, 256
 mammillaris lateralis, 226
 medialis, 226
 mammillary bodies, 225, 226, 246
 medialis dorsalis, 256, 259
 paracentralis, 260, 261
 parafascicularis, 260, 261
 parateanalis, 254
 paraventricularis, 225, 226, 227, 254
 posterior, 254
 preopticus, 226

Nuclei (cont.)

- pretectal, 413
- pulvinaris, 261, 262
 - inferior, 256
 - lateralis, 256
 - medialis, 256
- putamen, 446, 447
 - connections, 447
- reticularis, 176, 182, 256, 338, 448
- roof, 468
- ruber, 145, 146, 147, 175, 176, 181, 182, 256, 338, 448, 449
 - anatomy, 449
- Schwalbe, 157
- substantia nigra, 176, 181, 182, 448, 458
- subthalamic body, 446, 448
- supraopticus, 225, 226, 233
 - tectal, 469
- thalamic, 252, 253, 254, 255
 - anterior ventralis, 269
 - anteromedialis, 261
 - arcuate, 257
 - lateralis, 261
 - dorsalis, 201
 - posterior, 261
 - lateroventral, 255
 - medialis dorsalis, 269
 - posterolateralis, 257
 - pulvinaris, 261
 - ventralis, 255, 338
 - lateralis, 354
 - posterior, 257, 350, 354
- trigeminal, 257
- trochlear, 448
- tuber, 225, 226
- ventralis anterior, 254, 261
 - lateralis, 256
 - posterolateralis, 256, 258
 - posteromedialis, 256, 258
- vestibular, 145, 146, 157, 338, 466, 467, 481

Nucleolus, 38

Nystagmus, cerebellar, 487

vestibular, 179

O

Oblongata animal, 164

Occipital area, 306

eye fields, 413

lobe, 321

Occlusion, 102

reflex, 96

Olfaction, 316 *et seq.*

Olfactory bulb, 314

system, 314

Omentum, 100

Ophthalmoplegia, 186

Opisthotonos, cerebellar, 472

Oppenheim's sign, 385

Optic righting reflexes, 174

Otolith organs, 169

P

Pain, 2, 3, 10, 11, 16

cerebral cortex and, 351

endings, visceral, 99

fibre, 7

pathway in cord, 24

referred, 10, 100, 200

triple response and, 28

unlocalized, 24, 25, 26

unmyelinated fibres and, 25

Paleocerebellum, 466, 483

Paleothalamus, 254

Pallium, 274

Palsy, shaking, 457

Panting, 235, 442

Paraflocculus, 467, 476

Paramedian lobe, 465, 473

Paraplegia, extension, 140

flexion, 136, 140

Parasympathetic, acetylcholine and, 217

attacks, 249

chemical mediation, 67, 217

divisions of, 198

dorsal root outflow, 199

emotion and, 219

general action, 200 *et seq.*

homeostasis, 191, 218

system, 200 *et seq.*

anatomy, 198

bulbar outflow, 198

definition, 191

hypothalamic outflow, 198, 229, 249

postganglionic fibre, 196

sacral outflow, 199

tectal outflow, 198

Parietal lobes,

see Lobes, parietal

Parkinsonism, 457
 area 8 lesions, 413
 description, 457
 pathology, 457
 substantia nigra, 458
 Peptic ulcer, autonomic system and, 241
 Perikaryon, 38
 Peristalsis, inhibition of, 81
 Peritoneum, 99
 reflexes, 98, 99
 Perseveration, 406
 pH, *see* H-ion
 Pick's disease, 44
 Piloerection, 236
 Pilomotor reflex, 183
 system, 210, 211, 212, 436
 porcupine, 437
 Pituitary, diabetes insipidus, 232
 hypothalamus, 223
 innervation, 198, 229
 posterior lobe, 225, 229
 stalk, 230
 Placing reactions, 177, 357
 Polyuria, 223
 Porcupine, 212
 quill mechanism, 437
 Position sense, 364
 Positive supporting reaction,
 cerebellum, 476
 Postcentral area, 304
 motor responses, 351, 379, 380
 Posterior roots, visceral afferents, 27
 Postural reflexes, *see* Reflexes, postural
 Posture, doubled up, 98, 99
 upright, 100
 Potential, internuncial, 65
 Potentials, cord,
 origin, 64
 Prefrontal area, definition, 418
 Premotor area, 394
 Preoccipital area, 306
 Preparietal area, 304
 Pretectal area, 183, 184
 Problem box technique, 422
 Projection, cortical,
 macula, 327, 329
 occipital, 311
 vestibular, 338, 339
 Proprioceptive system, 148
 reflex effects, 154

Proprioceptors, 2, 6
 Psychiatric disturbances,
 hypothalamus, 243
 Psychic blindness, 343
 Psychogalvanic reflex, 435
 Psychology, physiological, 491
 Pulvinar, 261
 Pupillary dilation, 440
 reflexes, 183
 Pupils,
 area 8, 398
 Argyll Robertson, 180, 184, 188
 corpora quadrigemina, 181
 cortex and, 398
 cortical, 413, 437
 inequality, 413
 Purkinje cells, 469
 Putamen, 256, 446
 action potentials, 454
 athetosis, 454
 chorea, 454
 connections, 447
 forced circling, 451
 lesions, 451
 Pylorus, cortex and, 438
 Pyramidal tract,
 see Tracts, corticospinal
 Pyramids, autonomic system and, 329
 Pyramis, 467
 functions, 476
 Pyriform lobe, 227, 314
 excitability, 318, 320

Q

Quadruped attitude, 147
 Quill mechanism, 212
 porcupine, 437

R

Radiations, auditory, 339
 optic, 327
 visual, 327
 Radium emanation, 136
 Rami communicantes, discovery, 190, 196
 grey, 196
 white, 195
 Raynaud's disease, 208

- Reactions, lengthening, 150, 151, 408
 shortening, 150, 408
 Recall, 423, 425, 427
 Receptor-effector system, x
 Receptors, 1
 A1, 15
 A2, 15
 adaptation, 11
 all-or-nothing, 11
 B, 15
 C, 15
 chemical, 2
 cold, 4
 excitation, 11
 grasp reflex, 407
 hair, 4
 muscle, 149
 pressure, 9, 12, 16
 tendon organs, 152
 warm, 4
 Recovery heat production, 63, 64
 Recruitment, 47, 85, 95
 Red nucleus, *see* Nuclei, ruber
 Reflex figure, 123, 124
 time, central, 56
 Reflexes, abdominal, 412
 acceleratory, 172
 after-discharge, 96
 all-or-nothing principle, 91
 allied, 119, 141
 antagonistic, 122, 141
 antigravity, 103
 area 4, 384
 area 6 (upper), 411
 areas 9-12, 419
 arthritis, 98
 attitudinal, 167
 axon, 28
 Bainbridge, 161
 Berührungs, 349
 bladder, 99, 126, 127, 128, 129, 141, 440
 blink, 187
 cardiac, 242
 cardiovascular, 161
 carotid sinus, 199
 conditioned, 131, 357, 385, 424, 439
 rhinencephalon, 306, 314 *et seq.*
 consensual, 184
 copulatory, 187
 corneal, 187
 crossed extension, 81, 113, 152
 inhibition, 82, 132
 deafferentation, 152
 defecation, 129, 130
 deglutition, 157, 158
 delay paths and, 97
 d'emblée, 95
 ejaculatory, 125
 extension, 103, 104
 extensor thrust, 112
 flexion, definition, 51
 electrical response, 91
 forelimb, 118, 123, 124, 125
 fundamental experiment, 51
 galloping, 123
 galvanic, 27
 geotropic, 107
 grasp, 168, 405, 406, 407, 408
 area 6 (upper), 405
 centres for, 406
 corpus callosum, 406
 infants, 408
 labyrinth, 408
 postural reflexes, 407
 receptors, 407
 striatum, 407
 grooming, 405
 hiccough, 249
 hindlimb, 123, 152
 history, 51
 Hoffmann, 412
 hopping, 177, 179, 357
 intersegmental, 118, 119, 124, 141, 441
 labyrinthine, 111, 178, 406
 in man, 155
 otoliths and, 169
 semicircular canals, 169
 laughing, 182
 light, 183, 187, 188
 history, 180
 path of, 184, 185
 synapses, 184
 long circuiting in, 97
 magnet, 167
 Magnus and de Kleyn, 155, 163
 mass, 135, 142
 meningitis, 98
 myotatic, *see* Reflexes, stretch
 neck, 112
 negative supporting, 166

Reflexes (cont.)

- occlusion, 96
- overlapping of, 96
- panting, 235
- peritonitis, 98
- Phillipson's, 133, 134, 152
- pilomotor, 183, 187, 210, 236, 436
- placing, 176, 179, 357
- positive supporting, 165
- postural, 108, 407
 - history, 163
 - local static reactions, 164
- prepotent, 122
- proprioceptive, 154
- psychogalvanic, 435, 436, 443
- pupillary, 180, 183, 185
- reciprocal innervation, 99
- red muscle, 110
- respiratory, 160, 441
- rhythmic, 123
- righting, 179, 406
 - body on body, 174
 - body on head, 173
 - centres for, 175
 - cortex and, 176
 - labyrinthine, 173, 175
 - neck, 172, 173
 - optic, 174, 176
 - primates, 174
 - red nucleus and, 176
- Rossolimo, 411
- scratch, 24, 120, 121, 122
- segmental, 119, 166, 436
- sexual, female, 125
 - male, 125
- shifting, 166
- shivering, 236
- simultaneous combination, 121
- somatic, 119
- spinal man, 100, 131
- standing, 104
- stepping, 108, 123, 141, 154
- stomach, 99
- stretch, 104, 105, 135
 - after-discharge, 107
 - bladder, 441
 - cerebellum, 476
 - characteristics, 105
 - discovery, 104
 - flexor influence, 108
 - flexors, 112
 - functional significance, 107
 - inhibition, 105
 - latency, 107, 117
 - quadriceps muscle, 104
 - recruitment, 107
 - stepping, 108
 - sympathetic, 109
 - subliminal fringe, 93
 - subthreshold effects, 93
 - successive combination, 121
 - induction, 123
 - supporting, 476
 - swallowing, 158
 - sweating, 134, 235, 443, 444
 - tendon, 412
 - thalamic pattern, 172, 414
 - tonic neck, 167, 168
 - grasp reflex, 168
 - labyrinthectomy, 169
 - man, 155, 168
 - vasodilation, 235, 434
 - vasomotor, 161
 - spinal, 130
 - vertebra prominens, 168
 - vocalization, 181
 - vomiting, 157, 158
 - Whytt's, 180
- Refractory period, 57, 58, 61
 - absolute, 61
 - relative, 63
 - supernormal, 63
- Regeneration, axonal, 40
- Release phenomenon, 161
 - history, 143
- Remote control, 376
- Respiration, cerebral cortex, 398, 441
 - epilepsy and, 398
- Respiratory centre, 158
 - movements, 162
- Responses, cortical, infant monkeys, 373
- Responsiveness, subnormal, 89
- Restiform body, 467
- Reticulum, periterminal, 52
- Retina, structure, 322
- Rhinencephalon, 274
 - comparative physiology, 317
 - conditioned reflex, 318, 319
 - connections, 316
 - cytoarchitecture, 315, 316

- Rhythm, Berger,
 area 4, 373
 laminar coagulation, 373
 Righting reflexes, 172, 406
 Rigidity, *see also* Spasticity
 abdominal, 99, 100
 basal ganglia, 457
 cortical, 147
 decerebrate, *see* Decerebrate rigidity
 decorticate, 171, 172
 extrapyramidal, 457
 flexor, 126
 Rods, 322
 Roof nuclei, 469
 Roots, posterior (dorsal),
 antidromic action, 28
 ataxia, 149
 axon reflexes, 28
 bifurcation, 18
 centrifugal discharge, 29
 decerebrate rigidity, 147
 efferent fibres, 28
 ganglia, 20
 lateral division, 21, 24
 medial division, 21, 24
 motility, 149
 number, 20
 ratio of fibres to cells, 20
 regeneration, 29
 section, 31
 size, 20
 terminating *boutons*, 21
 termination, 22, 23
 unmyelinated fibres, 19, 20
 vasomotor fibres, 27, 28
 Rossolimo's sign, 411, 412
 Russell's uncinat fasciculus, 480, 481
- S
- Salivation, 198, 397, 439, 440
 Scarpa's ganglion, 170, 337
 Schiff-Sherrington phenomenon, 118, 124
 Schizophrenia, 439, 440
Schunkelreflex, 166
 Sclerosis, disseminated, 487
 Scratch reflex, 24, 121, 122
 Sella turcica, 325
 Semicircular canals, 170
 areas 3-1-2, 365
 area 5, 351, 365
 area 7, 351, 365
 cerebellum and, 487
 clinical work, 363, 364
 cutaneous, 352
 deep, 352
 encephalization, 358
 history, 348, 349
 parietal ablation, 358
 position, 364
 postcentral, 351
 precentral, 351
 roughness discrimination, 359, 360
 stereognosis, 358, 360
 topognosis, 364
 weight discrimination, 358, 359, 360,
 361
 Sensibility, gustatory,
 hippocampus and, 316
 remaining, 31
 tactile, 17, 24
 Septum pellucidum, 228
 Sex organs, innervation, 125, 215
 Sexual infantilism, 223
 patterns, 125
 Shaking palsy, 457
 Sham rage, 230
 Shifting reaction, 166
 Shivering, 236, 442
 area 4, 387
 Shock, spinal,
 bladder, 441
 Shortening reaction, 150, 162, 408
 Signs, neurological,
 Babinski, 101, 132, 384, 385, 412
 Chaddock, 385, 412
 fanning (Babinski), 412
 Gonda, 101, 412
 Gordon, 385
 Kernig, 98
 Mendel-Bechterew, 411
 Oppenheim, 385
 Rossolimo, 411, 412
 Schäfer, 385
 Simplex, lobulus, 473, 488
 Simultaneous combination, 121
 Single unit, *see* Motor unit
 Skin resistance, 435
 Sleep, 247, 248

- Sleep (cont.)
 - autonomic system and, 220
 - hypothalamus and, 221, 440
- Somatoceptors, 2
- Somatosensory functions, 264
- Somnolence, morbid, 440
- Sound, localization of, 343
- Spasticity,
 - areas 3-1-2, 410
 - area 4, 409
 - strip, 409
 - area 6, 394
 - area 6a (upper), 409
 - areas 9-12, 409
 - causes, 143
 - cortical, 409
 - digital, 384
 - strip region, 384
- Speech, Broca's area and, 426
 - cerebellar, 463, 484, 489
 - disturbances, 344
 - temporal lobe and, 346
- Spider monkey, 372, 473
- Spinal animal,
 - bladder reflexes, 126
 - excretory function, 126, 129
 - scratch reflex, 122
 - sexual reflexes, 125
 - sweating, 131
- Spinal cord,
 - incomplete section, 135
 - lateral columns, 443
 - tumours, 136, 140
- Spinal man, Babinski sign, 132
 - bladder, 133
 - case, 132
 - clonus, 135
 - crossed reflexes, 133
 - defecation, 134
 - extensor reflex, 131
 - flexor reflex, 131, 132
 - motion, 132, 133
 - Phillipson's reflex, 133
 - posture, 133
 - reflexes, 101, 133
 - sensation, 133
 - stretch reflex, 135
 - sweating, 131, 134
 - tonus, 133
- Spinal shock, 96, 123, 137, 141
 - baboon, 137, 139
 - bladder, 441
 - cats, 137
 - chimpanzee, 137, 139
 - dogs, 137
 - frogs, 137
 - history, 118
 - insects, 137
 - knee jerks in, 137
 - monkeys, 137
 - pyramidal tracts, 139
 - recovery from, 138
 - theories, 137
 - vestibulospinal tracts, 139
- Spindles, muscle, 8, 9, 11, 12, 13, 17
- Static reactions, general, 166, 167, 178
 - local, 164
 - segmental, 166, 178
- Stereognosis, 270, 358, 360, 364
- Stick-platform test, 423
- Stimulation,
 - antidromic, 36, 62, 63
 - basal ganglia, 449
 - caloric, 344
 - parietal lobes, 350
- Stimuli, definition, 11
- Stomach,
 - cortex and, 437, 438
 - innervation of, 99
 - reflexes from, 99
- Stretch reflexes, *see* Reflexes, stretch
- Striae of Baillarger, 274
- Striate cortex, 306
- Striatum, *see* Basal ganglia
- Strip region, 302, 384, 397, 409
- Strychninization, 354
 - areas 3-1-2, 352
 - area 4, 352, 353
 - area 6, 353
 - area 6a β , 354
 - cerebral cortex, 351
 - face area, 352
 - temporal, 343
 - thalamic, 266
- Subliminal fringe, 60, 93
 - definition, 59
- Substantia gelatinosa, 23, 24
 - nigra, 176, 182, 261
 - anatomy, 448
- Subthalamic body (Luys), 446, 448

- Successive combination, 141
 induction, 141
- Sulci, centralis, 261, 300
 frontalis, inferior, 261
 intraparietalis, 261
 occipitalis inferior, 261
 parieto-occipitalis, 261
 postcentralis superior, 261
 precentralis, 396
 inferior, 261
 superior, 261
 sylvii, 261
- Summation, 57
 central, 56, 59
 reflex, 56
 spatial, 13, 59, 79
 temporal, 13, 58, 79
- Supporting reactions,
 decerebellate monkey, 165
 man, 165
 negative, 166
 positive, 113, 166
- Suprasellar cyst, 156
- Swallowing, 162
 cortex, 397
 reflex, 158
- Sweating, 211
 anticipatory, 443
 area 6, 436
 cortex, 435, 443
 medulla, 442
 spinal man, 131, 134
- Sympathetic epilepsy, 249
- Sympathetic system, 189 *et seq.*, 200
 afferents, 27, 199
 anatomy, 193
 cervical, 201
 cortex and, 429 *et seq.*
 definition, 190
 eye and, 202, 203
 head, 202, 203
 heart, 204
 lacrimal glands, 203
 local reflexes, 27
 origin of term, 189
 postganglionic fibres, 196
 preganglionic fibres, 195
 sweating, 211
- Synapse, 79
 definition, 52
 origin of term, 52
 structure, 53
- Synaptic delay, 56, 57
- Synaptic terminals,
 see Endings and *Boutons terminaux*
- Syndromes,
 adiposogenital, 223, 237, 247
 flocculonodular, 483
 Fröhlich's, 223, 237, 247
 frontal areas, 427
 hemiballismus, 458
 Horner's, 180, 202, 203, 204
 lenticular degeneration, 445
 neocerebellar, 484
 paleocerebellar, 484
 thalamic, 266, 269
- Synergies, extensor, 400
- T
- Tabes dorsalis, 149
- Tail area, 372
- Tail, prehensile, 20
- Technique, Horsley-Clarke, 266
- Tectal nuclei, 469
- Tectum, 261
- Tegmentum, 183
- Temporal lobe, 259, 300, 305, 315, 337 *et seq.*
- Tendon organs, 15
 Golgi, 7, 8
- Tenon's capsule, 202
- Thalamic nuclei, 253 *et seq.*
 ventralis lateralis, 354
 posterior, 354
- Thalamic pattern, 172
 reflex, 414
- Thalamocortical projections, 261
- Thalamus, 252 *et seq.*
 action potentials, 354
 animal, 146, 164
 association nuclei, 259
 auditory projections, 259
 cortex and, 270
 derivation, 252
 general function, 267
 hemidecortication, 265
 muscle sense, 270

Thalamus (cont.)

- nuclei, 254 *et seq.*
- pain, 270
- strychnine activation, 354
- strychninization, 265, 266
- syndrome, 266, 269
- visual projections, 258

Thoracolumbar, *see* Sympathetic

Tinnitus, 345

Tongue, 397

Tonic labyrinthine reflex, 169

"Tonus," *see* Reflexes, postural

- see* Decerebrate rigidity
- history, 103
- somatic, 109
- sympathetic, 109

Topognosis, 364

Tracts,

- ansa lenticularis, 447
- cerebello-olivary, 467
- corticocaudate, 452
- corticohypothalamic, 327
- corticomesencephalic, 310
- corticonigral, 310
- corticopontine, 305, 310
- corticorubral, 310
- corticospinal, 305, 307, 382, 388
 - area 6, 372
 - autonomic effects, 444
 - bladder, 441
 - chronaxie, 372
 - definition, 307
 - divisions, 308
 - excitability, 372, 390
 - origin, 373
 - section, 373, 388, 401, 410
 - source, 307
 - terminations, 308
- corticostriate, 311
- corticosubthalamic, 310
- corticotectal, 186
- corticotegmental, 310
- corticothalamic, 310
- frontopontine, 435
- frontopontocerebellar, 310
- geniculocalcarine, 324, 327
- hook bundle, 467
- ipsilateral, 381
- lateral lemnisci, 258

Lissauer, 25

- mammillothalamic, 226, 261
- medial longitudinal bundle, 181
- olivocerebellar, 467
- opticus, 256, 261, 325, 326
- posterior, 137
- pyramidal, 136, 139, 207
 - decerebrate rigidity, 144
- rubrospinal, 388, 480
- Russell's uncinat, 480
- spinocerebellar, 23, 467
- spinothalamic, 23, 257, 265, 330
 - medial lemnisci, 257
 - posterior column, 257
- supra-opticohypophyseal, 98, 229
- temporopontine, 435
- vestibulospinal, 136, 137, 139
- Vicq d'Azyr, 227

Transmission, 65

- humoral, 67
- synaptic, 70 *et seq.*

Transneuronal degeneration, 325

Trapezoid body, 339

Tremor, basal ganglia, 457

- cerebellar, 471, 481, 482, 484, 486

Triple response, 28

Trunk ataxia, 475, 481, 484, 488

Tuber, cerebellar, 465

- cinereum, 225

Tuberculum acusticum, 279

- olfactorium, 314, 316
- excitability, 317

Tumours, area 16, 334

- brain, 364
- cerebellar, 98, 484
- pituitary, 324
- temporal lobes, 337, 345

Twitch, motor nerve, 92

- reflex, 92

U

Ulcer, peptic, cortex and, 438 *et seq.*

- hypothalamus and, 241

Uncinate attacks, 337, 345

Uncus, 345

Upright posture, 100

Urgency, 441

Utricle, 169

Utricular maculae, 173

Uvula, 466, 467

functions, 476

V

Vagina, cortex and, 375

Vasodilatation, 235

area 6, 434

Vasomotor system, cerebral vessels, 206

cortex and, 432

eye, 201

face, 203

paths in cord, 207

Ventricle, third, 223, 256

Vertigo, cortical, 399

Vestibular, *see* Nuclei

Vestibular function,

cortical, 343

Vestibular projection, 338, 339

Visceral pain, 99

Visceroceptors, 2, 6, 10

Vision,

acuity, 323

alexia, 334

binocular, 333

central, 323, 327

central scotoma, 328

cortex, 327

fields, 323, 324, 328

hallucinations, 334

hemianopsia, 323

history, 321

light, 332

macular, 326, 327

Meyer's loop, 327

object, 332

optic chiasm, 323

pathways, 325, 327

pattern, 332

phylogeny, 331

retina, 323

secondary neurons, 327

temporal lobe, 345

Visual system, geniculate bodies, 258

Vocalization, 397

Volitional movements, extrapyramidal, 412

see also Area 4

Vomiting, 157, 158, 162

W

Weakness, cerebellar, 485

Weight discrimination, 358, 359, 488

man, 364

Wernicke's aphasia, 366

Whytt's light reflex, 180

Wilson's disease, 445

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